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Radiation Therapeutics and Its Acute Effects on Human Body

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Abstract Present review article elucidate radiation generated effects on blood brain barrier, tissues, cells and organ systems of human body. Radiation is used to finish brain metastasis and tumor ablation but repetitive exposure of radiation induces multiple deformities almost in all tissues or organs. Low physiological dosage of radiation is provided to increase BBB permeability by loosing its structural integreity of BBB to administer the therapeutic drugs. But repeatitive use of radiation for diagnosis and therapeutic purposes generates severe side effects both instant and delayed. Irradiation causes instant effects on central nervous system (CNS) while late effects including demyelination, gliosis and necrosis, inflammation of photoreceptors, skin, lungs, hematopoietic cells and syndromes of bone-marrow depression and gastrointestinal damage. Radiation generates genotoxic effects in chromosomes, entangle its separation during cell division and disturb replication and transcription of DNA. Radiation exposure imposes intermediate effects like abnormal bonding between adjacent molecules while in germ cells radiation induces transient azospermia and failure of gonadal functions. Radiations also cause aberration of the blood vessels of the brain due to binding of radiation to radioreceptors and induce various syndromes and neurological diseases. In this review article an over view of all possible consequences of radiation exposure on human life and emphasize role of radio - protective medicines and other safety measures is presented. It also suggests use of combination therapies for cancer treatment rather than using radiation alone. No doubt combination therapies will prove better to ablate tumor at an earlier stage and may become landmark discovery in the field of cancer biology.

Keywords: *chemotherapy, radiation, radiation therapy, blood brain barrier, vascular permeability, acute biological effects, disorders and syndromes*

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1. Introduction

Radiation is used for both therapeutic and diagnostic purposes for treatment of cancer and tumor. This is used as an alternate to chemotherapy to destroy cancer cells and to enhance the survival of normal cells by restoration of cellular microenvironment. The diagnostic applications of ionizing radiation in medicine include the use of X-rays and radioisotopes in imaging. Similarly, limited and low dose radiation is used to destroy head and neck squamous cell carcinoma in targeted therapeutic strategies. For control of blood cancer in patient treatment course is included extracorporeal UV blood irradiation, intravenous laser blood irradiation and supra-venous blood laser irradiation. Ionizing radiation (IR) promotes cancer cell death through the creation of cytotoxic DNA lesions, including single strand breaks, base damage, crosslinks, and double strand breaks (DSBs) [1]. Radiation peneterates deep into the body layers and destroy toxic aggregates, reducing oxidative stress and protecting cells from aberrant metabolic damage [2]. Low dose for cellular irradiation is used to finish brain tumors mainly for increasing the permeability of therapeutic drugs across the blood-brain barrier. It makes easy reach of drug to the target area where it interacts with biomolecules and thereby modifying the tumour microenvironment [3]. For treatment of hepatocellular carcinoma stereotactic whole body radiation therapy is used [4]. Though it is considered safe but longer and repetitive exposure of radiation is harmful for tissue and normal body cells [5]. In comparison to adults and children undergoing radiation therapy, a complex and lengthy neurointerventional procedure is used and found to be more vulnerable to the effects of ionizing radiation. Radiation shows cumulative effects and causes vessel injury due to increase in contrast overload [6]. Similarly, exposure of natural radiation scattered in the environment to human being and other living beings generate metabolic effects mainly in all those who are not occupationally exposed to ionizing radiation from other sources during their daily work activity. Therefore, instead of diagnostic medical exposure, a largest part of the accumulated annual radiation dose is received by every person. Besides, the therapeutic benefits of radiation exposure, it is often harmful as it acts as a carcinogen and shows multiple adverse effects on cells and tissues (Table 1). Low radiation dose causes hemoglobin oxygen saturation of venous blood and impose photo-induced cellular changes which increases individual sensitivity of patient to radiation on blood. Pathophysiological effects of radiation and radiation

therapies are detailed out in this article with an essential need for development of biomarkers for both accidental and therapeutic injuries (Figure 1). This article also sketches all important consequences of radiation related injuries and their reversal in human and in animal models. However, to minimize the cumulative effects of radiation it signifies need of risk-adapted administration of conventional treatment modalities. In addition role of combination therapies, radioprotection and prophylactic measures should make mandatory to minimize the risk.

Table 1. Radiation therapy and its major side effects

Therapy	Radiation used	Therapeutic use	Side effects	Reference
Tumor irradiation therapy	Radiation sensitizer Cisplatin	To ablate brain tumors and brain metastasis	Causes severe alterations in blood plasma and cerebrospinal fluid, generates morbidity	[15,19,20]
Anti-VEGF therapy	temozolomide (TMZ) and/or radiation therapy (XRT)	Glial fibrillary acidic protein, and apoptosis, ant-angiogenesis	Permeability of the blood brain-barrier, reduced blood flow, and infarction, severe alterations in blood plasma and cerebrospinal fluid, Lesions, coagulation necrosis of white matter microangiopathy,	[5,8,16,17]
Whole brain radiation therapy (WBRT) and stereotactic radio-surgery (SRS)	20 Gy in 5 fractions	WBRT reduce cerebral metastasis	Deleterious effects in neurocognitive domains	[22]
Photon irradiation	2000 rad	Ablation of tumors	Effect blood-brain barrier permeability	[23]
carbon dioxide laser				
MRI and ultrasound	Waves	Scaning and tumor	necrosis, atrophy, calcification,	[25]
		therapeutics, combination	necrotizing leukoencephalopathy	
		therapy		
X-irradiation	20 Gy of 300 kV X-	Increasing the blood-brain	Causes severe damage in normal brain of	[26]
	rays	barrier permeability	experimental animals and patients	
Radiation-controlled	20 Gy	Decrease the complex	Causes radio necrosis occurs in normal	[28]
focal pharmacology		behavior of running	tissues	
Boron neutron capture	p-boronophenylalanine	Selective tumor irradiation	Focal hypoxia	[34] [35]
therapy BNCT	(BPA) or borocaptate			
	sodium (BSH) are used			
	as neutron capture			
	agents			
Whole-body	20 Gy in 5 fractions/	Induce the entry of BMDCs	Green fluorescent protein	[39]
irradiation	X-rays/ Low doses of	(bone marrow-derived cells)		
	roentgen rays	into the CNS myeloablative		
		chemotherapy		
Interstitial	125I	Increases blood-brain barrier	Causes significant alterations alter	[36]
radiotherapy	5- to 7-mCi	function	molecular and cellular mechanisms	
			hemato-encephalitic barrier in animals	
Radionucleides	platinum compounds	Treatment of glioblastoma,	Generate toxic effects at higher dose.	[40]
		improves progression-free		
		survival in patients		
Liposomal antitumor	Lipoplatin™ and	Reduction in malignancy F98	permeability of molecules through the	[40]
drugs	Lipoxal™, and	gliomas in Fischer rats	endothelial barrier	
	carboplatin			
PVB therapy	cisplatin, vinblastine,	Sensitizing effects against	PVB is tolerable	[15]
	and bleomycin	brain tumor		
Non-ionic surfactant	niosome	Entrapment on the absorption	Increase permeability of the blood brain	[179]
vesicle (noisome)		and distribution of	barrier, metabolic profile of the drug	
		methotrexate		
Radio-immunotherapy	T umor necrosis factor	Finish metastasis	Safe and has no side effect	[43]

1.1. Ionizing Radiation

Radiation is a form of energy that emits from a source and travels through space. As radiation emits from the source, there remains a possibility of deposition of a fraction of its energy in any matter it encounters. There are two main types of radiation i.e. ionizing and non-ionizing. Ionizing radiation contains enough energy which during interaction with an atom, it removes tightly bound electrons from the orbit and cause the atom to become charged or ionized [8]. It occurs in two forms either waves or particles. Ionizing radiation, on the other hand, is capable of stripping electrons from atoms and breaking chemical bonds, creating highly reactive ions (atoms or molecules that have an electric charge). In general, radiation is absorbed by matter, and show either excitation or ionization. Excitation occurs when the radiation excites the motion of the atoms or molecules and results the electron from an occupied orbital into an empty, higher-energy orbital. The most common types of ionizing radiation are alpha particles, beta particles, gamma rays, and x-rays. Ionization refers to the removal of an electron from an atom or molecule and a charged atom (or molecule) is called an ion [8]. On the contrary, non ionizing radiations are different types of waves such as radio waves that facilitate long distances communication via phones, televisions, and satellites. These individual waves have little energy to cause ionization (the stripping of electrons from atoms, which breaks the chemical bonds of molecules, which give matter structure [9]. Particulate radiation is also ionizing radiation which consists of atomic or subatomic particles (electrons, protons, etc.) and carries energy in the form of kinetic energy or mass in motion. Alpha rays consist of small positively charged particles called alpha particles. Being relatively large in size, alpha particles cannot pass very easily through solid matter. High speed alpha particles when colloid with gas molecules break electrons and generate intense photographic activity [10]. Beta particles are negatively charged particles which possess more penetrating power than the alpha particles. Gamma rays are not deflected even in the most intense magnetic or electric field. These are most penetrating of the three radioactive rays and are weak ionizers of gases.

Other potential sources of strong ionizing radiation are eruption of nuclear accidents or terrorist actions involving nuclear devices. The third type of ionizing radiation includes gamma and X rays (Table 1). These are electromagnetic indirectly ionizing, electrically neutral (as are all electromagnetic radiations) and do not interact with atomic electrons through Coulombic forces. Radionuclides are also source of radiation. These different forms of an element may be stable or unstable (radioactive). Isotopes are one or two or more forms of the same element having the same atomic number (Z), differing mass numbers (A), and the same chemical properties. The activity of a radioisotope is simply a measure of how many atoms undergo radioactive decay per unit of time. There are different international units of radioactivity. The SI unit of radioactivity is Becquerel (Bq) which is based on the rate of nuclear transformations. The Becquerel is defined as 1 radioactive disintegration per second. The old unit of radioactivity is Curie (Ci), which is based on the activity of 1 gram of radium-226, i.e. 3.7 x 10^{10} radioactive disintegrations per second. The activity of a radioisotope is simply a measure of how many atoms undergo radioactive decay per unit of time.

2. Therapeutic Uses

There are different modes of radiation exposure the human body according to the type of radiation emitted by source. Radiation waves mainly particulate materials incorporated into the body either through absorption in the skin or by inhalation and ingestion. Radiation is retained by the body which also displays significant radiation induced injury by specific tissues. The materials are concentrated inside whole body when radiation is repetitively used for therapeutic proposes. The primary factors which determine the type and degree of injury are the types and amounts of the isotopes deposited and the nature and energies of the radiation emitted from the source. Radioisotopes also enter inside body by inhalation, ingestion, and absorption through the skin. Following ingestion or inhalation, radioactive material may be absorbed into the blood stream, depending upon its solubility. Thus, radiation reaches the brain and alters patho-physiology of central nervous system (CNS) and generates delayed effects such as demyelination, gliosis and necrosis. Radiation also imposes pathogenesis like lesions, coagulation necrosis and obstructions in blood flow and causes infarction [11] (Figure 1). Radiations also cause aberration of the blood vessels of the brain due to its binding with radioreceptors and induce various syndromes and neurological diseases [12]. Further, it also causes significant alterations in molecular and cellular mechanisms and imposes allergic encephalomyelitis [13] and white matter microangiopathy in the spinal cord of experimental animals. High dose of radiation generates delayed effects in animals which are visualized few months to years after irradiation. Some of the possible delayed consequences of radiation are life shortening, carcinogenesis, cataract formation, chronic radiodermatitis, decreased fertility, and genetic mutations. Sometimes multiple effects of radiation appear in all tissues or organs due to significant decrease in immune tolerance of animal body. Radiation also generates autoimmune encephalomyelitis and neuroimmune diseases in experimental rats [14]. It also affects melatonin, a vital natural neuro-hormone that regulates our circadian rhythms and acts as a powerful antioxidant, anti-depressant and immune system enhancer. High radiation dose severely affect daily sleep/wake cycle, hormone production and immune system activity. It also affects blood pressure and disturbs heart rate cycle, metabolic rate, thermal regulation, and daily cycle of activity directly or indirectly through the autonomic system (Figure 1).

One of the most widely used methods of treating oncological patients is ionizing radiation therapy. Radiation beam causes damage to the cancer cells which help reduce cancerous mass and leads to recovery of the oncological patients. Despite deleterious effects of irradiation on body tissues, low level radiation exposure induce protective mechanisms by maintaining the physiological function are activated in early phase of

radiation injury [15] (Table 1). Thus, simple chemotherapy without surgery and radiation does not provide survival to glioma patients. Hence, new therapeutic approaches which favor osmotic, transient blood-brain barrier disruption followed by chemotherapy or immunotherapy are considered much better than the drug "tailoring" to render them more effective in barrier entry. Thus, genetic glioma manipulation may find more appropriate target of antiviral drugs due to which it penetrate the barrier. It is found investigated that radiation causes structural and functional disturbances in the hematoencephalic barrier and evoke adaptive immunity in exposed animals by transferring lymphoid cells [16]. Multiple exposure of low frequency radiation impose CNS related syndromes and induction of pathogenesis of lesions and selective coagulation of white matter in the spinal cord of animals [17]. ACE inhibitors and ARBs (angiotensin receptor blockers) have been shown to attenuate radiation injuries in animal models of lethal gamma irradiation [18] (Table 1).

Long term radiation exposure causes numerous side effects in patients which appear in the form of carcinogenesis and breakage of blood-brain barrier, with consequent extravasation of water, electrolytes, and plasma proteins from altered tumor microvessels. Space radiation also imposes negative effects on nervous system of pilots during space flight [19]. Moreover, insoluble radioactive materials are absorbed in extremely small amounts. These are eliminated fairly rapidly directly from the respiratory and gastrointestinal tracts. However, under certain circumstances, insoluble materials can be retained at or near the original site of deposition, e.g., in the lungs or in wounds, or may be translocated to regional lymph nodes, where again they will constitute an internal radiation hazard. More often, plasma proteins level can be used for assessment of radiation exposure at an earlier stage and become a conventional biodosimetry to give early diagnostic information to manage radiation casualty incidents effectively (Figure 2). It can aid in reducing of mass-casualty radiological incidents [20]. More often, to support clinical data multiple blood biomarkers, immunological, molecular and biophysical markers should developed.

2.1. Tumor Therapeutics

For tumor therapeutics patients get both diagnostic and therapeutic exposure of radiation. Low dose of radiation is used to destroy structural obstructions created by blood-brain barrier (BBB) to increase systemic blood flow or circulation by a continuous capillary network. Blood-brain barrier (BBB) is highly specialized structure that protects the neural tissue from harmful agents [21]. Its functional components are displayed by the perivascular boundary of neuroglial cells. BBB maintains a unique organ microcirculation because capillary endothelium has inter-endothelial tight junctions which prevent passage of large highly polar, water soluble molecules. Most chemotherapeutic agents do not effectively cross the blood-brain barrier, hence, radiation is used to lose the BBB and deliver therapeutic drugs for treatment. Thus, barrier protects brain from toxic substances and regulates transport of therapeutic drugs in to CNS entry. Therefore, to ablate brain tumors and brain metastasis whole-brain radiation therapy or cranial irradiation therapies are used to transfer drugs. The combination therapies are used for treatment of intracranial malignant germ cell tumor [22]. Though, *in situ* tumor irradiation increases blood-brain barrier permeability [23]. It also increases endothelial permeability clearance index, leukocyte-endothelial interactions and staining for vascular endothelial growth factor (VEGF) glial fibrillary acidic protein, and apoptosis [24] (Table 1). Neuroglial cells selectively exclude proteins and drugs from the brain parenchyma [25]. Though, radiation enhances endothelial permeability at low doses but its very high dose and long exposure can cause severe alterations in blood plasma and cerebrospinal fluid [26, 27]. Vascular permeability factor or vascular endothelial growth factor (VPF/VEGF) is a protein which is an important marker of human brain tumors. It serves as an extraordinarily potent inducer of both micro-vascular extravasations (edemagenesis) and assists in formation of new blood vessels (angiogenesis). It plays important role in tumor growth and its progression [28]. Thus, mass progression in tumor growth is a visible sign and symptom in patients that clearly display occurrence of deformities like cerebral edema, glioma, neuroblastoma and fluid-filled cysts [28]. Cerebral edema significantly increases and results in expansion of the cerebral interstitial space and contributes elevated intracranial pressure in brain tumors [28] (Figure 2) (Table 1).

2.2. Brain Radiation Therapy

Whole-brain irradiation (WBI) is used for treatment for brain metastases. Though it increases the drug permeability but induces brain injury and pathogenesis. It also causes significant increase in oxidative stress and inflammatory responses in the brain. Moreover, a selected higher dose of radiation is provided to ablate visible tumors in patients [29]. No doubt WBRT reduce cerebral metastasis but generate deleterious effects in neurocognitive domains [29] . Therefore, to reduce side effects of whole brain radiation therapy (WBRT) stereotactic radio-surgery (SRS) is also applied. Other important methods such as photon irradiation [30], carbon dioxide laser [31] and CT scan are used to treat tumor patients. But these methods impose adverse effects on human central nervous system during brain scanning done by MRI and ultrasound [32]. In rats, irradiation dose of 60 Gy causes disruption of the BBB and induce severe diffuse vasculature leakage, and does severe loss of the capillary network, cortical atrophy and white matter necrosis. Similarly, X-irradiation affects pharmacokinetics of drugs by increasing the blood-brain barrier permeability [33]. Its over dose causes severe damage in normal brain of experimental animals and patients [34]. Hence, to lower down risks during treatment, radiation-controlled focal pharmacology should be used to minimize damage and radio necrosis in normal tissues [35]. Same method is also used to concentrate neuropharmacologic agents in any selected portion of the brain to dislodge BBB integrity in that area by irradiation [36]. Post treatment reversal or repair of radiation injury is also seen between 6 and 12 weeks when sub-lethal doses are provided (Table 1).

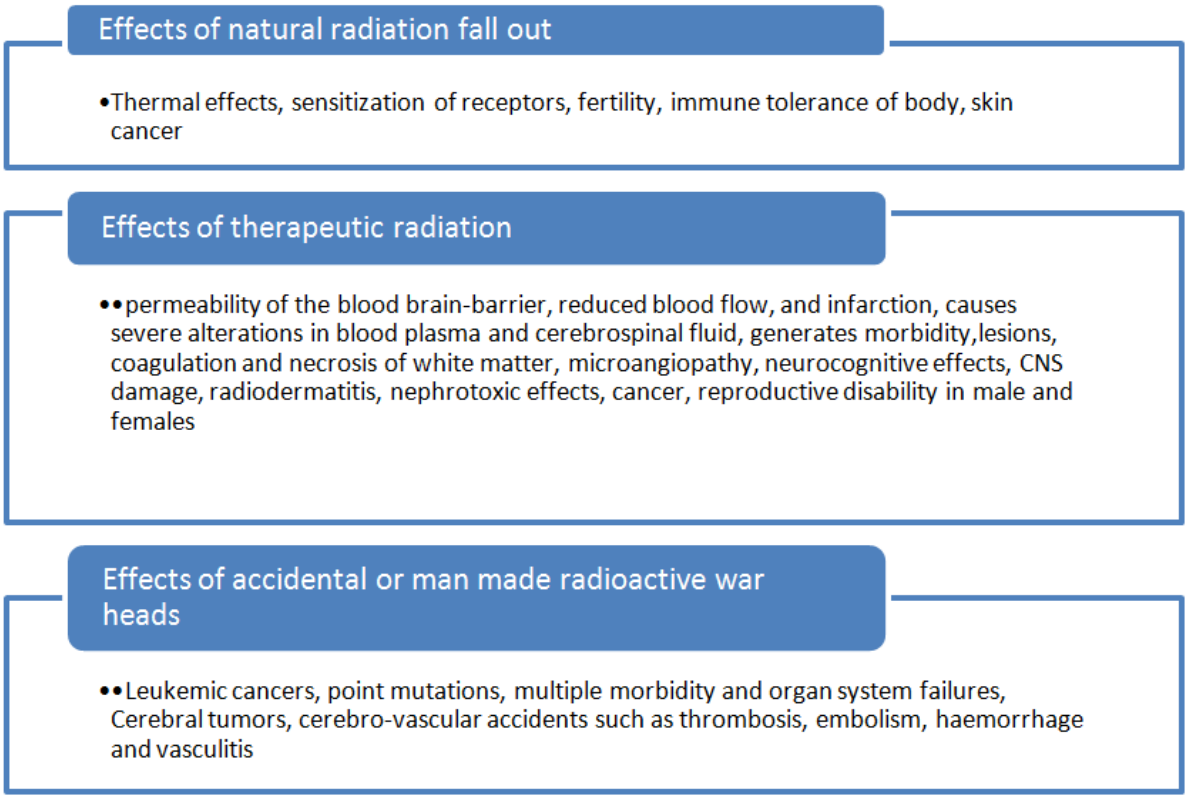

Figure 1. major physiological effects of natural and artificial radiation on man

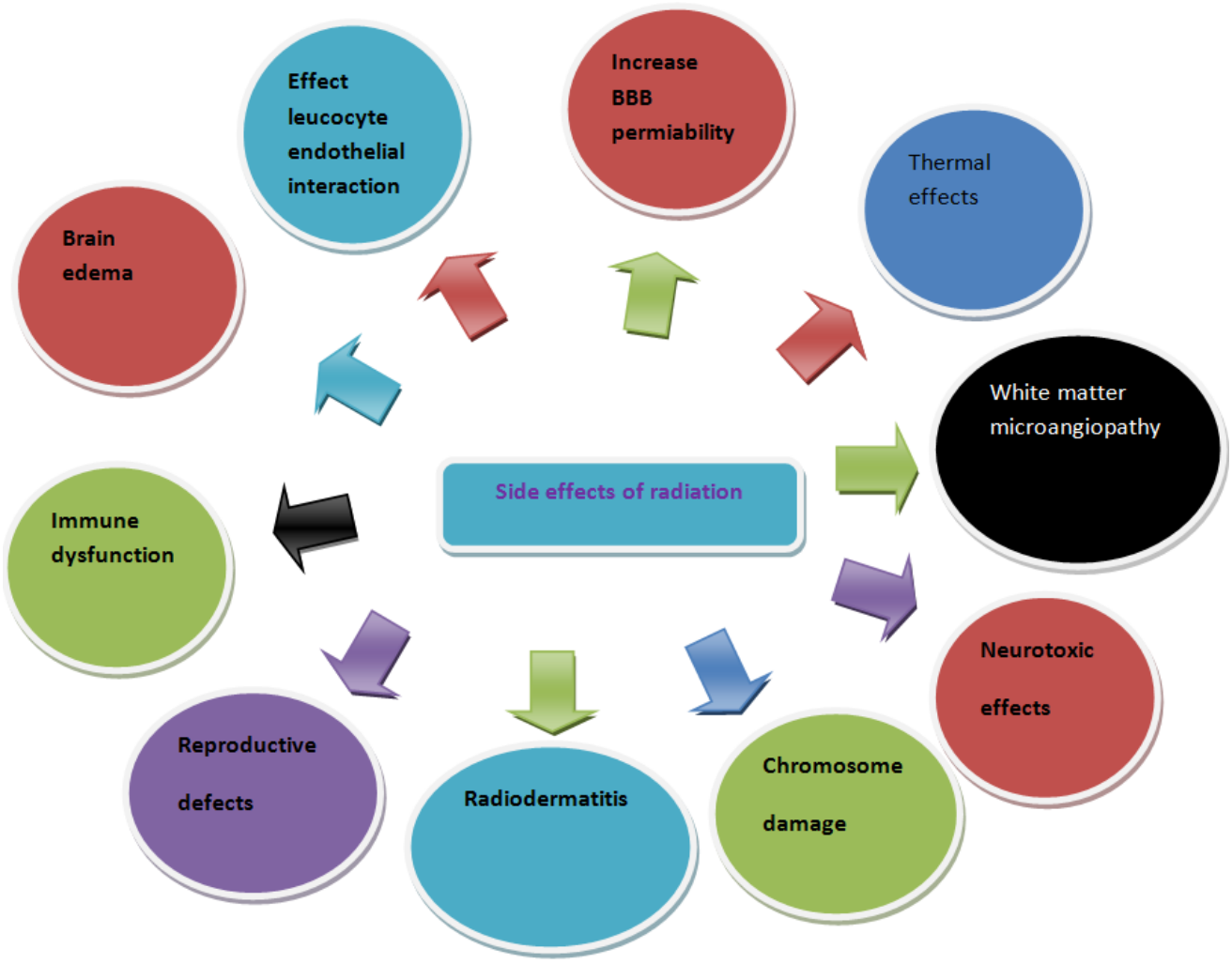

Figure 2. various biological effects generated in man after repetitive therapeutic radiation exposure

However, selective irradiation is provided for the treatment of intracranial, sinus, nasopharyngeal, intraorbital and intraocular tumors [37]. But WBI generates noxious stimuli that result in oxidative stress and evoke inflammatory responses in the brain with altered capillary permeability [38] (Figure 2). Sometimes it also causes a heavy damage to the normal brain and its surrounding tissue. Similarly, X-ray users/survivors showed extensive cortical atrophy, loss of neurons, and widespread leakage of the blood-brain barrier (BBB). Long term exposure of X-rays forms avascular, collagenous tumor scars [39,40]. Myeloablative chemotherapy regimen severely causes brain damage and blood-brain barrier (BBB) modification. This therapy increases the capacity to induce the entry of BMDCs (bone marrow-derived cells) into the CNS and is found more feasible for therapies for brain-related disorders. Similarly, boron neutron capture therapy (BNCT) is used for treatment of brain tumors [41]. It is a binary method in which selective tumor irradiation [42] is done by using p-boronophenylalanine (BPA) or borocaptate sodium (BSH) as neutron capture agents [43]. It increases the tumor cell uptake, limits the toxicity and delivers the best concomitance effect with radiotherapy. Similarly, interstitial radiotherapy is applied by using 125I that increases blood-brain barrier function [44], while low doses of roentgen rays play important role in humoral mechanisms and change status of the hematoencephalic barrier [45]. Similar treatment of glioblastoma with platinum compounds modestly improves progression-free survival in patients but these radionucleides generate toxic effects at higher dose. Similar effects are also seen after antenatal ethanol exposures on the function of the hemato-encephalic barrier in experimental animals [46]. Therapeutic irradiation of the head and neck region is used for control of tumor growth and for palliation of tumor mass effect. In addition, stereotactic surgery is intensively done to treat the tumors. Systemic use of corticosteroids, hyperbaric oxygen therapy free-radical scavengers showed some efficiency in treatment, especially in acute phase. Injection of bone marrow cells from green fluorescent protein (GFP) in transgenic mice is resulted in completely repopulating the hematopoietic niche in the circulation and in hematopoietic organs (thymus and spleen). Thus, it can be concluded GFP(+) cells only enter the brain following whole-body irradiation [47]. Therefore, to finish neoplastic affects both drugs and low intensity radiation doses are applied in radiation therapy Moreover, radiation induced pathophysiology and its recovery is an important thrust area in clinical radiotherapy research (RT) (Figure 3) (Table 1).

2.3. Antitumor Drug Therapy

Liposomal formulations, i.e. Lipoplatin™ and Lipoxal™, and carboplatin are used for reduction in malignancy F98 gliomas in Fischer rats [48]. These liposomal formulations showed modest accumulation of drugs in tumor cells and largely reduced the toxicity and allowed a better exploitation of the anti-cancer activity of radionuclides. Although the liposomes Lipoplatin™ and Lipoxal™ have shown a similar ability vis-a-vis carboplatin, to accumulate in brain tumors which shows better therapeutic effects [48]. Hence, to reduce toxicity, platinum drugs are encapsulated in liposome for controlled drug administration which are administered intra-venous, intra-arterial or combined with blood brain barrier disruption. Similar therapeutic effectiveness is also seen in combination chemotherapy done by using cisplatin, vinblastine, and bleomycin (PVB therapy) by Taira et al., 1986 [49]. PVB chemotherapy using cisplatin is much tolerable and shows sensitizing effect and antitumor activity [49]. But it creates poor permeability through the blood-CSF barrier and can be used to treat germ cell tumors that may often disseminate in the cerebrospinal fluid. But intracranial malignant germ cell tumors such as embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma in pediatric age groups are very hard to treat because assimilation of high radiation during radiotherapy. Moreover, intra-arterial route is used for transient opening of the blood brain barrier with mannitol. Similarly, increased fluorescein transport is also displayed size-dependent increase in BBB permeability that was found correlated with the severity of immunotoxicity. For better therapeutics of tumor patients fine nanomaterials loading pharmaceuticals are used. These nano-materials were found to be more efficient and reliable tool for improving the bioavailability of a gene or drug delivery system [50]. Similarly, inhaled fluorescent magnetic nanoparticles increase drug distribution in mice brain [50] while silver nanoparticles (Ag-NPs) interact with the cerebral microvasculature induced blood-brain barrier inflammation and increased permeability in primary rat brain micro vessel endothelial cells [51]. Interestingly, nanotechnologies do not produce adverse effects on human health and the environment; hence, these are used for safe delivery of drugs by using different routes (Table 1).

Anticancer agents are useful for treating brain tumors, but sub therapeutic concentrations due to decreased blood-brain barrier (BBB) penetration limit their effectiveness. Effective chemotherapeutics for primary systemic tumors have limited access to brain metastases because of the blood-brain barrier (BBB) [52]. Hence, treatment of metastatic brain lesions remains a central challenge in oncology. Most chemotherapeutic agents do not effectively cross the blood-brain barrier, it is widely accepted that radiation remains the primary modality of treatment. Interestingly, combination treatment with temozolomide and Herceptin enhance anti-tumor effect and increase survival in mice. More specifically, radiation therapy alters endothelial barrier functions such as trans-endothelial electrical resistance (TEER), morphological effects, and localization of adhesion and cell junction proteins and permeability of molecules through the endothelial barrier. WBRT is used to finish cerebral metastasis and show different effects in combination to neuroprotective drugs or alone [29]. Similarly, Gamma radiation (5 Gy) induced a rapid and transient decrease in TEER at 3 h where cells often detached from the monolayer leaving gaps [53] (Table 1).

2.4. Anti-VGEF Therapy

Vascular endothelial growth factor (VEGF) is associated with vascular proliferation within the peritoneum. These factors restrict inhibition and slowdown vascular proliferation with subsequent loss of

membrane function in peritoneal dialysis patient. Effective chemotherapeutics for primary systemic tumors have limited access to brain metastases because of the blood-brain barrier (BBB). Therefore, to finish metastasis tumor necrosis factor (TNF) or lymphotoxin (LT) or anti-VGEF is administered intravenously which increase the permeabilizing capacity of the BBB at cerebral metastases sites [52]. Subsequently, to locate the TNF activity on metastasis gadolinium- diethylenetriaminepentaacetic acid, horseradish peroxidase, or radiolabeled trastuzumab (111) In-BnDTPA-Tz is injected intravenously after 2 to 24 hours [52]. Interestingly, human brain metastases displayed a similar TNF receptor profile compared with the mouse model. Predominant vascular TNFR1 expression is used as marker to locate brain micrometastases and facilitate tumor-specific access of chemotherapeutic agents. Similarly, tyrosine kinase inhibitor, sunitinib maleate shows an anti-VGEF effect that is used for medication in patients of renal cell carcinoma with extensive abdominal metastasis. This inhibitor shortens the thickness of the peritoneal membrane and prevents angiogenesis [54]. It also finishes gut-derived organisms which causes peritonitis. It aptly stabilizes intestinal metastasis and prevents the transmural migration of bacteria from the gut [54] (Table 1).

2.5. Convection-enhanced Delivery

Convection-enhanced delivery (CED) is used to deliver large therapeutic molecules across the blood brain barrier. It is an innovative therapy that is used for the treatment of non-neoplastic neurological diseases such as tumors in different locations of the brain mainly in cerebral hemispheres [55]. It is relatively less invasive delivery method because of liposomal preparation is used to transfer biologics into dorsal root ganglia [56]. It was found effective against murine proneural glioblastoma [57]. Moreover, intra-neural convection enhanced delivery of AAVrh20 is used for targeting primary sensory neurons, [56]. Novel implantable catheter system with transcutaneous port for intermittent convection-enhanced delivery is used for carboplatin transfer to recurrent glioblastoma [58] (Barua et al., 2014) and in diffusing intrinsic pontine glioma [59,60]. Hence for tumor therapeutics different CED methods i.e. intraputaminal [61], image-guided [62] and intra-tumoral convection-enhanced delivery are used for destruction and removal of tumor [63]. In addition, microfabricated catheter for intraparenchymal is used for 111 delivery [64] while image-guided interventional therapy for cancer treatment with radiotherapeutic nanoparticles [65]. CED is also used for biodistribution of intracranially infused radiolabeled interleukin-13 receptor-targeted immunotoxin IL-13PE by SPECT/CT in Glioma [66]. CED is also used for AAV2-PrPshRNA in prion-infected mice [67]. Recombinant immunotoxin-based therapy is used to treat glioblastoma in murine model [68]. O(6)-methylguanine-DNA methyltransferase-siRNA/liposome complex is delivered by convection-enhanced delivery to rat and porcine brain [69] while unilateral intraparenchymal delivery method is used for drug treatment in swine [70]. More exceptionally, KATP channel agonists are used to increase the anticancer drug delivery to brain tumors [71] (Table 1).

3. Use of Anti-angiogenic Agents

The human vasculature includes a vast network of micro-capillaries networking the body and is a major target for non-carcinogenic effects of space radiation in the body. The human vasculature is critical to healthy functioning of the tissues of the body and a major factor in maintaining homeostasis in the endothelial barrier. Its pathology is not only a primary event in a range of neurodegenerative diseases but also an important influencing factor. Blood-brain barrier (BBB) is highly specialized in order to sustain the neural tissue [53]. The vasculature is maintained by angiogenesis regenerating vessels assist in repair of blood-brain barrier when it is damaged by agents such as space radiation. The relevance of angiogenesis inhibition in the treatment of glioblastoma multiforme (GBM) should be considered in the unique context of malignant brain tumors, while treatment of other tumor types may be improved by combining chemotherapy with anti-angiogenic drugs. These methods are used for inhibition angiogenesis in GBM that may antagonise the efficacy of chemotherapeutic drugs by normalizing the blood-brain barrier function. Although angiogenesis inhibition do make significant reduction in GBM patients, but to raise anti-tumor effects is very difficult. Thus anti-angiogenic treatment in patients with glioblastoma multiform is an important area of research in CNS biology [72]. Often, peripheral glioma cells remain at risk in adjacent healthy brain as serum components leak through the blood brain barrier (BBB). If glimoa cell migration is regulated by Vn receptor integrins therapeutic benefit may be derived from pharmacological integrin inhibition in combination with photon irradiation [73]. More specifically, anti-angiogenic agents, such as bevacizumab (BEV), can induce normalization of the blood brain barrier, which may influence the penetration and activity of a co-administered cytotoxic drug. Intracranial irradiation treatments of human glioma BEV and temozolomide (TMZ) and/or radiation therapy (XRT) showed good recovery in patients and increase in an overall survival [74]. Irradradiation of cranium also affects the pharmacokinetics of drugs in plasma and cerebrospinal fluid (CSF) [75]. Similarly, Eribulin treatment may be beneficial for breast cancer patients with brain metastases progressing after whole brain radiation therapy [76]. Contrary to these, fingolimod had different beneficial effects during different stages of DTH, reducing BBB breakdown and lesion development. It causes brain tissue damage whilst reducing lymphocyte recruitment when BBB breakdown remain apparent, it may reduce demyelination independent of lymphocyte infiltration behind an intact BBB [77]. High linear energy transfer (LET) (1 GeV Fe) shows relative biological effect and low LET 1 GeV protons effect developing vessels and alter their morphology 5 days after exposure. Undoubtebly significant differences in morphology were due to distinct mechanisms of inhibition. Cells exposed to protons failed to make connections with other cells. Conversely, cells exposed to Fe ions extended cellular processes and made connections to other cells but did not develop a central lumen [53]. Microtubule and actins cytoskeletons showed differences indicating motility at the extending tips of endothelial cells which is inhibited by protons but not Fe

ions. For high LET ions, the cells fail to complete angiogenesis by not migrating and forming tubular structures but it never happens in case of low LET ion treatments [53]. This complexity of response opens up possibilities of greater control over angiogenesis and the resulting pathologies during coincident exposure or therapy [53] (Table 1).

4. Inhibition of Vasculogenesis

The human vasculature is critical to healthy functioning of the tissues of the body because it plays major role in maintaining homeostasis in the endothelial barrier. It includes a vast network of micro-capillaries networking within the body tissues and cells. It is a major target for non-carcinogenic effects of space radiation in the body [21,53]. Its pathology is not only a primary event in a range of neurodegenerative diseases but also an important influencing factor in many other diseases. The vasculature is maintained by angiogenesis regenerating vessels assist in repairing of blood-brain barrier after damaged by agents such as space radiation. More often, lack of vasculature due to the inhibition of re-growth of vessels leads to a negative feedback and generate further pathologies [21,53]. Contrary to this, in vitro tissue culture angiogenesis is inhibited by ionizing radiation [21,53]. More specifically, stereotactic radiosurgery and stereotactic body radiotherapy are used to finish metastatic renal cell carcinoma [78]. It is also used in angiogenic regeneration. The angiogenesis inhibition in the treatment of glioblastoma multiforme (GBM) is an important aspect and unique in context of malignant brain tumors. More often, other tumor types may be improved by using combining chemotherapy with anti-angiogenic drugs which inhibit angiogenesis. But there is a possibility that GBM may antagonise the efficacy of chemotherapeutic drugs by normalizing the blood-brain barrier function. Hence, drugs which show angiogenesis inhibition and raise anti-tumour effects in patients make an important thurst area of research [72].

5. Major Biological Effects of Radiation

5.1. Effects on Brain Vasculature

The human vasculature is major factor in maintaining homeostasis and healthy functioning of the tissues of the body because it contains endothelial barrier. This blood-brain barrier (BBB) is highly specialized in order to sustain the neural tissue [53]. Moreover, radiation is used for chemotherapy of glioblastoma [79], and for selective permeabilization of the blood-brain barrier at sites of metastasis [52]. Presence of the tumor in a rat intracranial model alters the response of normal tissues to irradiation [80]. It was observed that presence of tumor appeared to reduce the volume of rolling leukocytes [53] but has little effect on leukocyte-endothelial interactions and astrogliosis [80]. It is true that presence of tumor alone increases permeability but cell adhesion functions and BBB morphology is altered after selective irradiation. Low and selective dose of radiation increases tissue permeability, leukocyte-endothelial interactions, and astrogliosis but higher dose of radiation is harmful to major cell functions. It depends on dose or intensity of radiation provided to the patients. On the contarray, unirradiated tumor and peritumoral tissue showed poor clearance. Radiation reduces the presence of VEGF in peritumoral normal tissues but did not affect the amount of apoptosis in the normal tissue. For optimization of the route and radiotherapeutic effects on glioblastema administration of radionucleide based drugs such as platinum drugs are administered to the patients in appropriate amounts [81]. Interestingly, such treatment of glioblastoma with platinum compounds modestly improves progression-free survival and may cause less toxic effects in reduced dosage. These compounds facilitate improvement in the antineoplastic effect and reduce toxicity if platinum drugs encapsulated in a liposome [81]. Similarly, gamma radiation (5 Gy) induces a rapid and transient decrease in trans-endothelial electrical resistance (TEER) after 3 h of radiotherapy dose of 2 Gy. It generates morphological effects, does defaulted localization of adhesion and cell junction proteins that alters permeability of molecules through the endothelial barrier. Though different species of ionizing particles inhibit vasulogenesis [21,53] but treatment of metastatic brain lesions with radiation dose remains a central challenge in oncology [29] because high dose of radiation shows acute effects on human brain mainly on endothelial barrier function [21,53]. Often, radiation generates severe acute effects different animals and human on BBB barrier function (Figure 3) (Table 1).

5.2. Effect on BBB Permeability

Irradiated cells may show both increased and decreased permeability. Radiation changes within the lipid bilayers of the membrane that may alter structure and function of ionic pumps. This may also make changes in the viscosity of intracellular fluids associated with disruptions in the ratio of bound to unbound water. Such changes would result in an impairment of the ability of the cell to maintain metabolic equilibrium and could be very damaging even if the shift in equilibrium is quite small. It has been reported that radiation exposure severely affects normal permeability functions of blood-cerebrospinal fluid and blood-brain barrier [82] in experimental animals [83]. Similarly, X-rays [84,85] and roentgen rays irradiation also causes changes in the functional status of the hemato-encephalic barrier [84] and effect permeability of the blood-brain barrier [85]. Identical effects of X-rays irradiation on the permeability of the blood-brain barrier were noted in presence of 5-hydroxytryptamine in normal and adrenalectomized rats [86]. BBB permeability severely affect uptake of therapeutic radionucleides [87] and distribution of drugs inside animal body [88]. Radiation imposes structural changes in the hemato-encephalic barrier and induces exogenous hypoxia [89,90]. This effect is due to radioprotectors occuring in the functional state of blood-tissue barriers in animals exhibiting limited mobility [91]. RF is also emitted from mobile phones significantly that opens the BBB in animals and make leakage of albumin from blood vessels in inappropriate locations (neurons and glial cells surrounding the capillaries) in the brain [92] (Figure 3). This leakage

indicates damage in blood vessels and visualizes that brain has lost some of its protection. Mobile phone radiation disturbs intra-cellular mechanisms and alter the permeability of the blood-brain barrier, and generate stress response and effects of hsp27 (increased expression and activity). All these physiological changes caused by hsp27 phosphorylation indeed take place in endothelial cells (stress fibers' expression, cell size/shape changes). These incidents, when occurred repeatedly (on daily basis) over the long period of time (years) become health hazard because of the possible accumulation of brain tissue damage [92]. Thus, mobile phone radiation induces expression and phosphorylation (activity) of stress protein hsp27 that might be the molecular mechanism regulating blood-brain barrier permeability possibly, the cell apoptosis. A seven day exposure to the radiation from a GSM-900 mobile phone increased blood–brain barrier permeability in mammalian brain [93]. It is true that radiation exposure imposed delayed effects and causes a marked aggravation of the clinical and pathological signs of EAE. The severity of the disease may be a consequence of the effect of irradiation on the CNS vascular bed and impaired blood-brain barrier [94]. It significantly decreases uptake of therapeutic radionucleides [95]. Introduction of ACTH with radiation dose accelerate distribution of radioactive phosphorus P32 [96,97] (Figure 3) (Table 1).

Suppression of blood-brain barrier permeability to hydrophilic tracers was most pronounced at brain temperatures exceeding approximately 40°C and demonstrated to be temperature dependent. It not only increase permeability of hydrophilic molecules mainly [^{14}C] labeled sucrose in the cerebral cortex, hypothalamus, cerebellum and medulla [98] but also generated structural effects due to thermal microwaves or ambient heat-induced disruption of the blood-brain barrier [98]. Similar, morphological changes were also displayed in cerebellum of neonatal rats exposed to 2.45 GHz microwaves [99]. Similarly, microwaves, thermal heat and photo-radiation generate thermal effects which lead to initiate multiple deformities in man [100]. Radiation exposed cells showed deep-stained pyknotic small cells presented electron dense nuclei with clumped chromatin, extrusion or disintegration of the nucleus, ruptured nuclear membrane, and the vacuolization of the cytoplasm. Eventually these cells became phagocytosed by surrounding EGL cells. In addition, Purkinje cells were also displayed disorderly arrays of rough endoplasmic reticulum (RER) instead of orderly stacks of parallel arrays. It proves that microwave radiation may interfere with early genesis of cerebellar microneurons and alter the metabolic status of Purkinje cells but it might be reversible (Table 1).

5.3. Effect on Vascular Permeability

The mammalian blood-brain barrier (BBB) consists of endothelial cells, linked by tight junctions, and the adjoining pericytes and extracellular matrix. It helps in maintaining a highly stable extracellular environment necessary for synaptic transmission and protects nervous tissue from injury. It is true that therapeutic radiation increase the permeability from normal to low but both hydrophilic and charged molecules become potentially detrimental. Similarly, electromagnetic pulse (EMP) shows effects on blood-brain barrier permeability and tight junction (TJ)-associated protein expression in rats [101]. Extremely low frequency magnetic fields (ELF) increase the vascular permeability in the circumventricular organs of adult rat brain [102]. Long exposure of biological systems to high magnetic fields (MFs) produces several side effects. However, low MFs assist in tissue recovery in chronic wounds, and do re-establishment of blood circulation after tissue ischemia or in necrotic tissues and it never become possible in high MFs radiation exposure. Though, MFs reduces epileptic episodes and tissue angiogenesis in tumor patients ELF shows vasodilator effect and increase BBB permeability to non-liposoluble substances [103,102]. Exposure of low levels of radiofrequency electromagnetic fields (EMF) increase the permeability of the BBB for drug macromolecules but increase brain temperature by more than 1°C which is reversible [103]. Contrary to this, low frequency EMF, do not cause tissue heating or show any thermal effect. Long-term exposure of magnetic field (MF), insulin, and their combination increase blood-brain barrier (BBB) permeability in a diabetic rat. Both DM and MF increase BBB permeability; in combination, but presence of insulin decreases their effect on BBB [104]. DM increases MABP but MF causes no additional effect. Similarly, whole brain radiation therapy (WBRT) creates palliation, yielding a median survival time of only 3 to 6 months. WBRT alone, or in conjunction with other treatment may affect cognitive function and impose slight morbidity risks [105]. Similarly, exposure of rats to low-field (0.15 T) magnetic resonance imaging (MRI) increases blood-brain barrier (BBB) permeability [106] (Table 1).

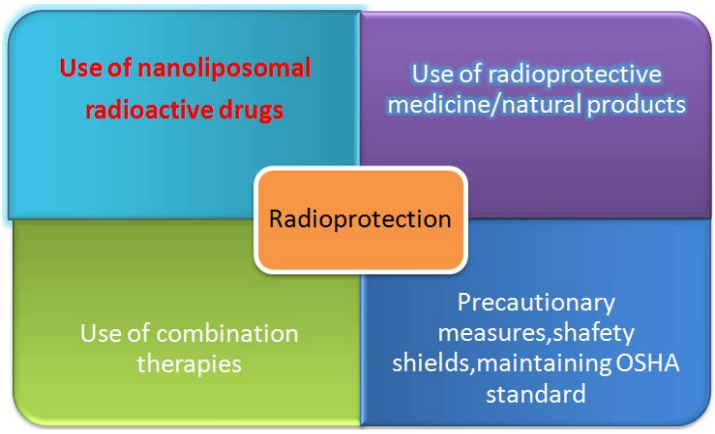

Figure 3. Radio-protective measures to avoid undesirable effects of radiation in man and experimental animals

Radiation induces thermal effects in living organisms and biological materials which impairs the integrity of the blood brain barrier (BBB) and massively alter the functions of the BBB by making changes in the ultrastructural locations. Radiation treatment increases the permeability of pharmacologically active substances [107] and effect the activity of phosphatases. It activate the pinocytotic vesicular transport, glycogen deposition in astrocyte cytoplasm [107]. Radiation affects both qualitative as well as the semi-quantitative and quantitative passage of substances across the damaged BBB [107]. Response of the BBB to ionizing radiation is found to be dependent on both dose to which the brain is exposed properties of the tracer [107]. Exposure to high doses of ionizing radiation (of the order of 25 Gy) results in an immediate precipitous decline in cerebral blood flow (CBF) due to changes in endothelial ultrastructure. It adversely affects the ability of the brain to regulate its blood supply. An acute whole body irradiation excess of 1000 cGy radiation dose generates early transient incapacitation (ETI) in an exposure time of 5 to 10 minutes. Hence, shielding should be done to reduce the behavioral effects of radiation mainly to tap rising incidence of convulsions (Figure 3).

Exposure to ionizing radiation (100 rad), lithium chloride and ethanol as unconditioned stimuli was found enough for the acquisition of a conditioned taste aversion in the rat [108]. These severe perivascular cellular alterations get prevented by dose ranges for the pretreatment with HR. Both compounds have shown antiedematous effect of HR on the radiogenic cell oedema of the perivascular neuropile, and work as membrane protector [109]. 0-(beta-hydroxyethyl)-rutosides affect glycolytic pathway [109] and affect middle cerebral artery (MCA) thrombosis on the integrity of the blood-brain barrier (BBB). Nimustine (ACNU), a drug that can cross the blood brain barrier, is administered before radiotherapy. It radically improves the survival of patients with primary central nervous system lymphoma (PCNSL) [110]. Similarly, both thiotepa and its active metabolite tepa more efficiently cross the blood-brain barrier [111]. 0-(beta-hydroxyethyl)-rutosides shows radiation-protective effects like anti-edema in the rat brain [112]. It help restores terminal blood supply in vascular endthelium. Hypofractionated stereotactic radiotherapy (hfSRT) is used to finish metastasis and brain tissue necrosis in adult rats. Its impact on blood-brain barrier can be observed by recording signal changes on high-field magnetic resonance imaging [MRI]) [113]. Partial-brain irradiation with hfSRT (Novalis System) can be used in small animals for histopathologic analysis of confirmation of repositioning accuracy. To control brain tumor fluid balance and pH position emission tomography can be used, which are metabolically perceived. Glucocorticoid and radiation treatment induce simple passive exchange of alkalotic or osmotic active molecules between plasma and tumor interstitial space. This generates anti-edema effect and enhances the transport of 82Rb [114]. They are helpful in metabolic control mechanisms of neuropathologic effects which are correlated with dose and observation time. Local radiotherapy is used to preserve neurological function but surgical intervention provide good results in epidural spinal cord metastasis [114] (Table 1).

5.4. Effects on Hematopoietic and Digestive System

Whole-body irradiation, severely injure brain tissues disturb membrane receptors present on nerve cells. Radiation heavily interacts with other cells of hematopoietic and digestive system and create profound disturbance in the cell kinetics and impose various syndromes of bone-marrow depression and gastrointestinal tract. But both hematopoietic and gastrointestinal system show fairly rapid cellular replacement rates and normally contains cell populations in overlapping stages of maturation and differentiation from primitive stem cells to mature functional cells [115]. These cells possess the power to repair and replace the injured or damaged cells. Interestingly, stem cells of the various cell lines of both the systems (HP and GI) are found highly sensitive to radiation whereas the mature functional cells are relatively resistant. Following radiation exposure, injured stem cells are never differentiated or transform in to mature cells. On the other hand if mature cells die or otherwise lost they will not get replaced and the overall population of cells in the system will decrease and no repair or replacement becomes possible. Radiation also damage human salivary gland stem cells and ameliorate hyposalivation [116] (Table 1).

On the contrary, high dose of radiation causes severe damage and impose irreversible changes and no possible recovery in hematopoietic cells. But in case of gastrointestinal syndrome, the cell kinetics of the villi can be restored and the radiation injury remains repairable because of genesis of new cells and replacement of old injured cells. Cells of GI tract show recovery and results in a gradual return of a mature, afresh functional population of cells. Likewise, bone marrow transplantation restored the intestinal mucosal barrier after total body irradiation in mice [115]. BMT enhance general hematopoietic and immune system recovery restores the intestinal immune system and improves intestinal mucosal barrier functions [115]. In GI tract radiation affected cells can be replaced by newer cells in a short span of time. But this property does not occur in hematopoietic cells. Normally cell replacement of damage cells is an important natural process that can be induced in other tissues and cells to get rid of radiation effect. Failure of a particular organ system or single system may or may not lead to death of the animal, but multiple organ failure. Many physiological, biochemical and molecular dysfunctions and patients display clear radiation related morbidities (Figure 3).

Transplantation of bone marrow-derived mesenchymal stem cells ameliorates theoacetamide induced liver fibrosis in rats after regional hepatic irradiation. Bone marrow-derived mesenchymal stem cells (BM-MSCs) can control liver fibrosis [117]. Radiation accelerates hematopoietic subsyndrome (AH-ARS) and acute radiation syndrome (ARS and GI-ARS). It induces SIRS (systemic inflammatory response syndrome) and FN (febrile neutropenia), and greater lung damage, compared to H-ARS [118]. JNJ7777120 compound, a histamine H4 ligand showed protection in radiation-induced damage to the hematopoietic system, small intestine and salivary glands in rats [119]. Histamine shows radioprotective effect on highly radiosensitive tissues. JNJ7777120

treatment diminishes mucosal atrophy and preserved villi and the number of crypts after radiation exposure. It reduces apoptosis, atrophy of SMG and DNA damage in intestinal crypts. JNJ7777120 also reduced radiation-induced aplasia, preserving medullar components and reducing formation of micronucleus by accelerating bone marrow repopulation and completely reversed radiation-induced reduced salivation, conserving glandular mass with normal histological appearance [119] and reducing apoptosis and atrophy of SMG. JNJ7777120 exhibits radioprotective effects against radiation-induced cytotoxic and genotoxic damages in small intestine, SMG and hematopoietic tissues [119]. Fungal melanin is a highly effective radioprotector against WBI and the probable mechanisms of radioprotection are due to modulation in pro-survival (ERK) signaling, prevention of oxidative stress and immunomodulation [116]. GM-CSF promotes the survival and activation of macrophages and granulocytes, as well as dendritic cell differentiation and survival *in vitro* [120]. TS-mobilized progenitor-containing PBMC acts as a bridging therapy by inhibiting radiation-induced apoptosis, enhancing cell proliferation, and inhibiting bacterial translocation in irradiated mice [120]. HIR preconditioning enhances the effect of BM-MSCs in improving thioacetamide-induced liver fibrosis in rats by promoting their homing and repopulation. BM-MSCs function by inhibiting transforming growth factor-β1-Smad signaling pathway in the liver [117]. It is an important strategy to alleviate or treat intestinal radiation toxicity [115]. It is a novel bridging therapeutic approach that involves the infusion of TS-mobilized hematopoietic progenitors following acute radiation injury to humans. Ex-RAD ameliorates radiation-induced peripheral blood cell depletion, promotes bone marrow recovery, reduces p53 signaling in spleen and protects intestine from radiation injury [121]. Radiation induces damage to the sinusoidal endothelium; impose endothelial injury, microthrombosis, subendothelial damage and cytokine activation. These processes lead to concomitant progressive hepatocellular dysfunction and subsequent fluid retention and renal impairment [122]. IL11 is orally provided to protect the intestinal mucosa from radiation damagecause this compound is beneficial as a mitigating agent in subsiding the radiation effect 24 h after radiation exposure [123]. Administrations of MSCs (mesenchymal stem cell) control systemic inflammation in pigs. It reduces both expression of inflammatory cytokines and macrophage recruitment *in situ*, and augmented interleukin-10 expression in rectal mucosa [124]. MSC injections also cut down radiation-induced fibrosis by reducing collagen deposition and expression of col1a2/col3a1 and transforming growth factor-β/connective tissue growth factor, and by modifying the matrix metalloproteinase/TIMP balance. MSCs treatment represents a promising therapy for radiation-induced severe rectal damage [124] (Figure 3) (Table 1).

5.5. Chromosomal Damage

Radiation massively affects the integrity of DNA structure and generates complete breaks of the nucleotide chains, by imposing point mutations. Radiation induced DNA breaks and chromosomal aberrations arise when replication meets base excision repair [125] (Figure 4). Radiation hits hard at gene structure and massively affects gene activity in somatic and reproductive cells. Radiation exposure and its assimilation inside body reach the cell nucleus severely damaging the chromosomes and accelerating the rate of spontaneous mutations that is the inherent tendency of each cell. Irradiated chromosomes become sticky due to formation of temporary or permanent inter-chromosomal bridges preventing normal chromosome separation during mitosis and transcription of genetic information. This results in occurrence of unequal division of nuclear chromosome material between daughter cells. It also aids in formation of nonviable abnormal micro nuclei in irradiated cells. Very high radiation generates intermediate effects, such as abnormal bonding between adjacent molecules and alterations in viscosity. UV-A-irradiation causes genetic instability [126] and imposes genotoxicity [127]. Similarly, radionuclides such as uranium generate chromosome aberrations and increase chromosome fragmentation [128] and impose carcinogenesis [129]. But DNA damage checkpoint pathway promotes extensive resection and nucleotide synthesis to facilitate homologous recombination repair and genome stability [130] (Table 1).

High-dose irradiation results in cell cycle arrest, apoptosis, and developmental defects during *Drosophila* oogenesis [129] and induces double-strand DNA breaks [131]. It induces oxidative DNA damage [132], cell death in human diploid fibroblasts by promoting cell cycle progression and inhibiting apoptosis [133]. Radiation also imposes mitotic catastrophe in FANCD2 primary fibroblasts [134] and and impose cytogenetic abnormalities [135] and onset mutagenesis in newborns and adults [136]. Most adverse effects are seen in affected people from bombing radiation or radioactive fission. Contrary to this, RNF8-independent Lys63 poly-ubiquitylation prevents genomic instability in response to replication-associated DNA damage [137]. Histone H3 lysine 14 (H3K14) acetylation facilitates DNA repair in a positioned nucleosome by stabilizing the binding of the chromatin Remodeler RSC (Remodels Structure of Chromatin) [138]. Similar protective effects are seen in treatments of citrus and rosemary extracts on UV-induced damage in skin cell model and human volunteers [139]. Repetitive exposure of whole-body irradiation causes temporary and permanent genetic changes in neonates as well as in adults. Radiation also imposes multiple sicknesses and evokes various syndromes in affected or exposed patients. Partial body irradiation for limited time period is used for tumor therapy. Radiation exposure starts progression of cervical cancer [140] due to DNA or chromatin damage [141]. Conclusively, continuous low dose of radiation causes point mutations which occur at slightly higher rate in population of cells, than spontaneous point mutations occuring naturally. No doubt radiation induced mutations persist for longer time and become the abnormal genetic burden of future generations (Figure 4) (Table 2).

5.6. Effect on Reproductive System

Radiation exposure in higher animals generates reproductive abnormalities related to gonadial dysfunction. In male animals low doses of radiation cause abrupt decrease in sperm counts. Commonly a transient azoospermia appear at sub-lethal radiation a dose which lasts for several months to several years. Contrary to this, effects of low

doses of radiation are recoverable and natural fertility can be restored. This recovery depends upon the regeneration of elements of the stem cell population which remain as resistant part of the germ cell cycle. In exposed males radio-resistant fixed stem cells are transformed and new spermatogonia can be formed. Specifically, when chromosome aberrations are produced in somatic cells, the injury is restricted to the specific tissue or cell system but any aberration in germ cells, reflect in next coming generations. However, *in vitro* culture, the stem cells of the germ cell line do not develop into mature sperm cells or ova, and no abnormality is transmitted to next generation of cells. Therefore in exposed animals radiation prevents fertilization; if it succeeds then embryo is not viable because of inhibition of cellular differentiation. If chromosome damage occurs very slight and no loss of genetic material takes place, the offspring will remain viable and survive, but abnormalities may persist for longer time and will transfer to the next succeeding generations. More often, long-term exposure of radiation (radiofrequency 2.4GHz) emitted from Wi-Fi towers affect testes functions [142], spermatocytes [143], sperm production in males and reproductive ability in male rats [144]. Similarly, ELF-EMF exposure affects reproductive abilities of male *Drosophila melanogaster* [145], impose infertility [144] and prohibit erectile function in males [146]. It also affects oogenesis in Drosophila [147]. Similarly, ionizing irradiation-induced radical stress stalls live meiotic chromosome movements by altering the actin cytoskeleton [148] while photo radiation acts as double-edged sword in regulating sexual development of *Hypocrea jecorina* (*Trichoderma reesei*) [149] (Figure 4) (Table 2).

Cell growth gets retarded, because of progressive formation of inhibitory metabolic products and/or alterations in the cell microenvironment due to radiation exposure usually after latent period. Enormous cell death is observed following heavy radiation exposure. This is due to pyknosis, karyolysis, protoplasmic coagulation, karyorrhexis and cytolysis. Longer radiation exposure and high dose affect cell differentiation in neonates. Stem cells are less sensitive to radiation but differentiating cells somewhat lesser sensitive to radiation. Mitosis may be delayed or inhibited following radiation exposure, but as soon as radiosensitivity decreases, cellular differentiation restarts. Both platelets and mature megakaryocytes are relatively radio-resistant. Similarly, stem cells are also radio-resistant but its transforming immature stages are highly radiosensitive. However, regeneration of thrombocytopoiesis after sublethal irradiation takes but it normally lags behind both erythropoiesis and myelopoiesis. Moreoften, the renewal system works mainly in GI tract in crypt and villus where epithelial cell formation, migration and replacement take place.

6. Radiation Induced Delayed Effects

6.1. Carcinogenesis

Repetitive whole body irradiation induces carcinogenesis [150]. It increases the chances of cancer or accelerates its appearance and invasion, or both. Radiation induces myeloid leukemia [151] or leukemogenic effects which are seen in survivors after heavy radiation fallout from radioactive bomb. Repetitive high dose exposure of radiotherapy evokes clinical appearance of the cancer [151] for which few genes are responsible [150]. Cancer may be seen after latency period of months or for several years which is different for different organs e.g. bone tumors. Carcinogenesis depends upon the dose and type of radiation emitted by the radionuclide, dose, and tissue type and exposure period. Similarly, type of cancer also depends on factors such as radiation duration, dose, age, and species. Multiple carcinogenesis signs and symptoms are displayed by skin tissue after therapeutic exposures of several thousand roentgens. Irradiation also showed delayed effects whose latency period for skin cancer is of 12 to 56 years. Ionizing radiation induces multiple deformities and more than one kind of leukemia [151] and also generates malignant fibrous histiocytoma [152]. Photo-radiation also causes disruption of the circadian clock and imposes severe risk of malignant tumors [153]. Ionizing radiation results in somatic mutions, DNA damage and show genotoxicity [154], while ultraviolet radiation-induce skin cancer [155]. It imposes severe carcinogenesis that depends on heredity, age and hormones [156]. X-rays modulates several signaling pathways resulting in transcription factor activation [157]. These also activate NF-κB in HEK cells in a dose-dependent manner which inhibit apoptosis and promote carcinogenesis. IN radiation exposed cells activation of NF-κB takes place by the canonical pathway and it was found to be quicker than by the genotoxin- and stress-induced pathway [157]. Ionising radiation often results in oxidative stress, epigenetic changes and genomic instability [158] and show altered gene expression responses in human lung fibroblasts [159]. Rutin a plant natural product exhibits radio protective effects and inhibits UVB radiation-induced expression of COX-2 and iNOS in hairless mouse skin: p38 MAP kinase and JNK as potential targets [160].

6.2. Cataract Formation

All types of ionizing radiation may induce cataract formation including infrared [161]. Time delay between the exposure and the onset of cataract after exposure to a threshold dose was observed. It implicates that either IRR cataract is photochemical or there is a time delay in the biological expression of thermally induced damage [161]. Similarly, neutron irradiation also induces cataract formation, even at relatively low doses. Cataract formation initiates at the posterior pole of the lens and continues until the entire lens gets affected. It is not lost in opacity that depends on the dose as well as the type of radiation. The threshold for detectable cataract formation takes place after having exposure of 2 Sv (sievert) (200 REM (roentgen equivalent, man)) radiation doses and 15 Sv (1500 REM) for protracted doses. In addition, radiation-induced nitrosative symptomatic stress is also observed in lens tissue. UVR-B exposure of double cataract threshold dose induces a subtotal loss of epithelial cells across the whole anterior surface of the lens [162].

But similar damage in epithelium is repaired by epithelial cell movement from the equator towards the lens sutures, in a retrograde direction to regular epithelial cell differentiation [162] (Table 2).

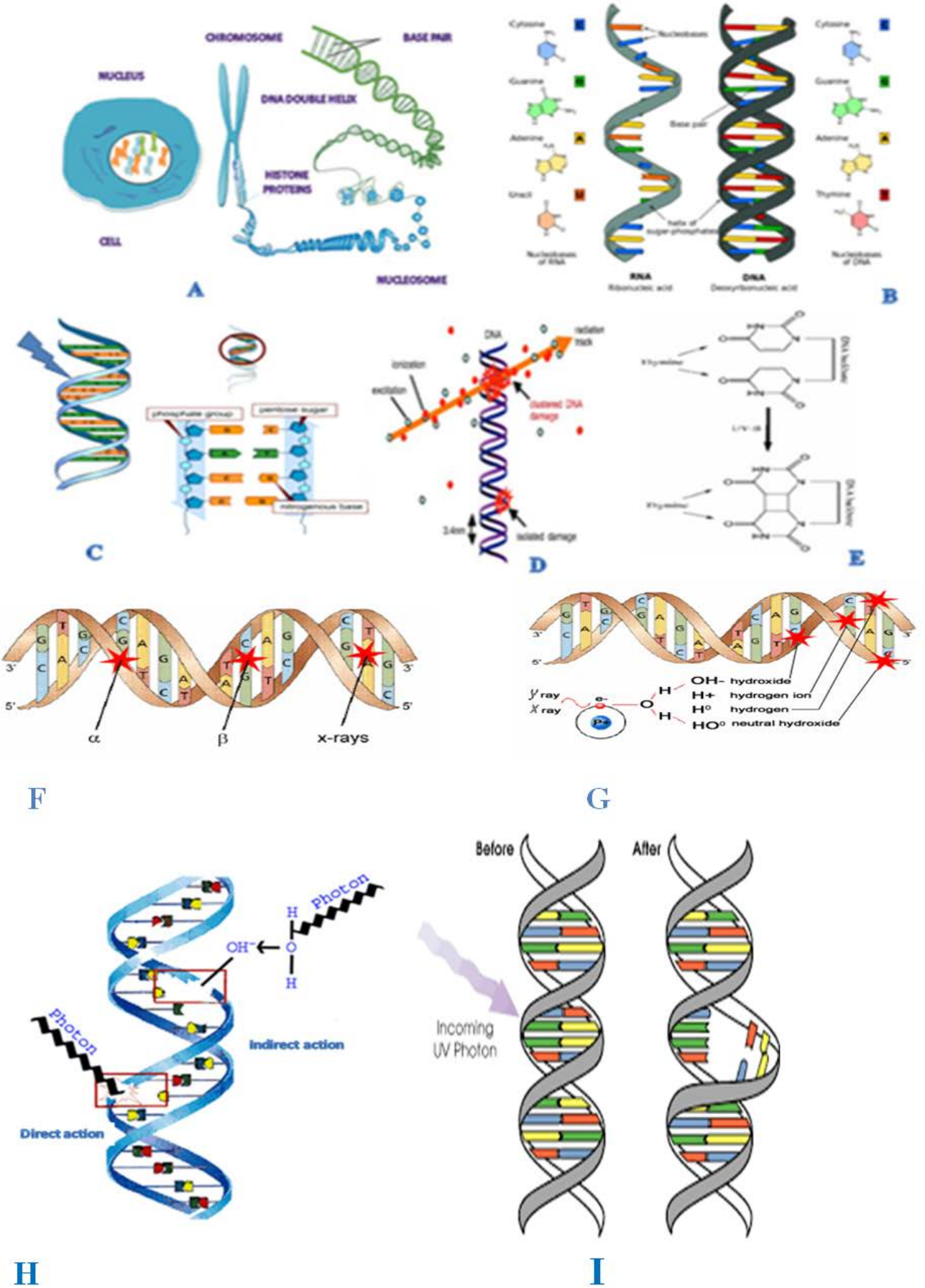

Figure 4. showing direct and indirect action of radiation on DNA breakage

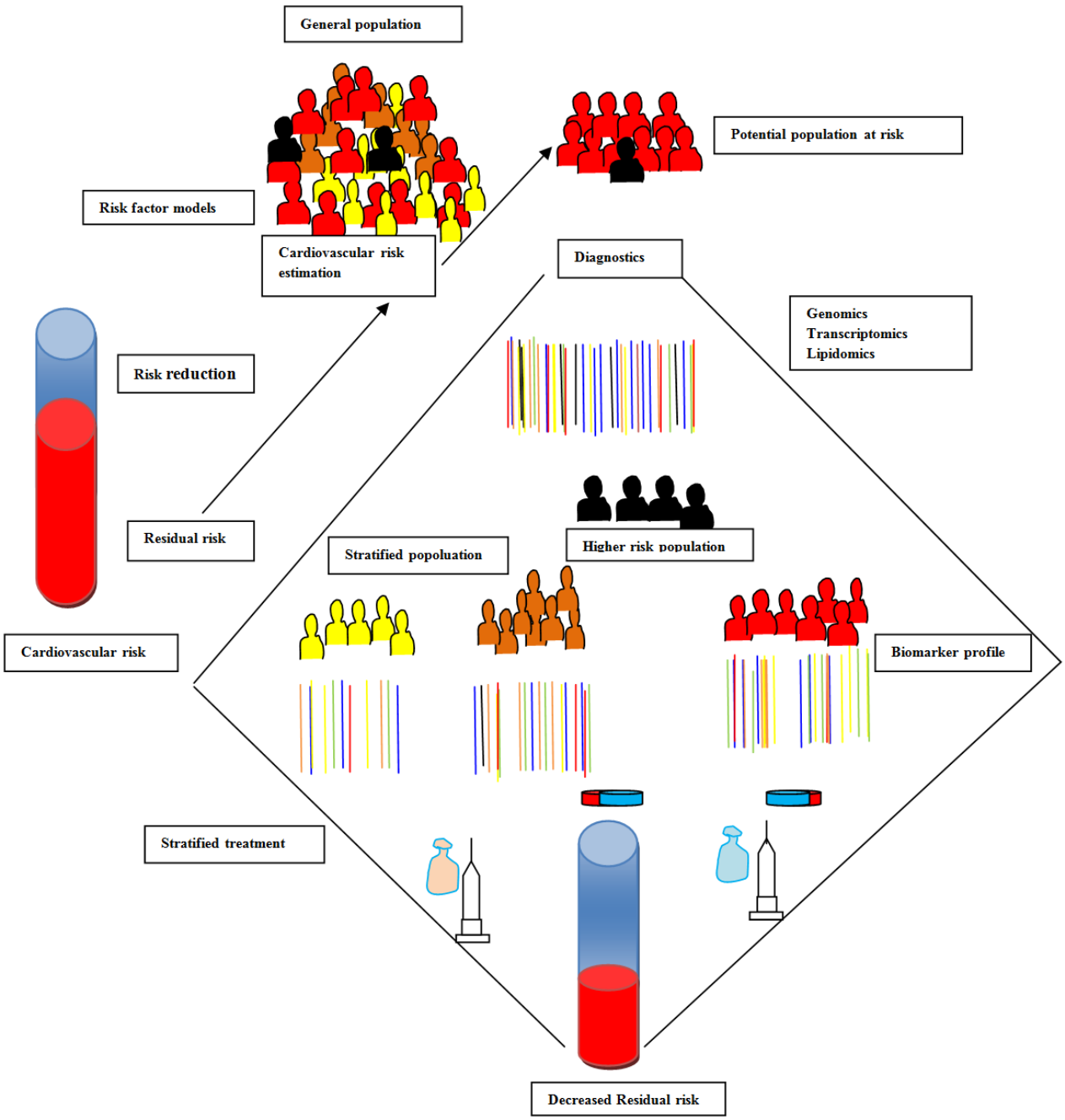

Figure 5. Showing potential population at risk due to radiation exposure with stratified risk prediction in models and risk profiling

6.3. Effect on Integumentary System

High radiation emission after nuclear combat or heavy radioactive arsenal or fallout from Chernobyl severely affects skin. Heavy radiation exposure in soldiers generates chronic radiodermatitis. Consequently, its fall out causes heavy contamination of bare skin and induce skin ulceration in combating soldiers and in radiation exposed population. Exposure to ultraviolet radiation (UVR) evokes development of skin cancers in humans. The ultraviolet B (UVB) radiation wavelength (280-320 nm), in particular, causes DNA damage in epidermal keratinocytes, that results in pre-malignant mutations [163]. Hence, interactions between dermal fibroblasts and keratinocytes play a role in epidermal repair and regeneration after UVB-induced damage [163]. Interestingly, the expression and phosphorylation of p53, act as a key player in the regulation of keratinocyte cell fate post-irradiation. It is also influenced by fibroblast-produced factors [163]. Radiation induces genotoxicity [164], and fibrosis in Murine Skin Model [165] and affects tissue architecture and immortalization status. It generates genotoxic responses in human body and makes alterations in DNA repair fidelity [164]. Ultraviolet B (UVB 290-320 nm) radiation has been used in the treatment of different skin diseases. Monochromatic Excimer Light (MEL represents a new source of narrow-band UVB emitting at 308 nm) is used in treatment of chronic and recurrent skin diseases because of their potent and selective immunosuppressant action [166] (Table 2). Moreover, sub-lethal whole-body irradiation does not develop delayed, irreversible changes in skin or no dermatitis occurs in exposed person [163] (Figure 5).

Ionizing radiation such as gamma or beta particles is insoluble material which contaminates the intact skin and generate external hazard. In controlled condition during

whole-body radiation therapy it does absorb into the blood stream and become an internal hazard. Contrary to this severe skin syndromes are generated in exposed person if they are subjected to pass through heavy fallout contamination. This can be easily prevented by using radio-protective shielding, while clothing and washing exposed areas of skin. Because wound site remains close to the dermis hence, contamination may cause a serious problem. In such cases, a small but measurable fraction of the material is cleared from the wound site by lymphatic drainage and even after that a large portion of radioactive material remains trapped in the regional lymph nodes. It leaches/ drains out slowly with the time from the wound sites by microscopic lymph channels. Usually, soluble radioactive material is absorbed through wound sites and proliferated to the body organs and tissues according to the usual metabolism of the stable isotope of the element (Figure 5).

More specifically, cutaneous radiation syndrome is the delayed consequence of localized skin exposure to high doses of ionizing radiation. Adipocyte derived stem cells injection can improve tissue regeneration through secreted factors in skin cells [167]. Hence, mesenchymal stem cells secretome optimization can be an appropriate strategy to treat this syndrome. Sonic hedgehog, protein facilitates cell proliferation and angiogenesis, and can be used as a candidate molecule to treat skin syndromes [167]. Infrared-C Radiation increases the skin temperature and thereby increases thermal effects, pain and stroke in patients [168]. Ionizing radiation selectively reduces skin regulatory T cells and alters immune function [169]. It also induces inflammation with resultant specific loss of regulatory T cells from the skin and generates a hyper-responsive state with increased delayed type hypersensitivity *in vivo* and CD4+ T cell proliferation *in vitro* [169]. Ionizing radiation affects the expression of Toll-like receptors 2 and 4 in human monocytic cells through c-Jun N-terminal kinase activation [170]. Ionizing radiation affects expression of TLRs and cellular responses to ligands THP1 monocytes (human monocytic leukemia cells) and THP1-derived macrophage cells (macrophage-like cells), which are induced by culturing in the presence of phorbol 12-myristate 13-acetate. X-irradiation increases the expression of TLRs in THP1 and cause decrease expression in macrophage-like cells. Ionizing radiation modulates ligand-responsive TLR expression through the JNK pathway, depending on differentiation state [170] (Figure 5).

6.4. Effect of Ultrasound

Blood brain barrier (BBB) inhibits the entry of the chemotherapeutic agents into the brain, therefore, ultrasound is used to open blood brain barrier for drug delivery to brain [171]. Ultra Sound influences the BBB and forcefully open BBB and cause increase in cerebral hemorrhage with multiple side effects. Glioblastoma multiforme (GBM) is the most aggressive brain neoplasm, and patients have a poor prognosis after radiation and chemotherapy. Therefore, for safe disruption of BBB, controlled low frequency ultrasound is used [172]. It is used to increase permeability of blood brain barrier and assist in transporting large amount of drug across the BBB [173]. Ultra sound is used for focal distribution of drug in nervous tissue but few biophysical factors influencing its application [174]. It is used to treat brain tumors to fasten the distribution and dynamics of small molecule leakage into targeted regions of the brain. Often, low-frequency ultrasound-mediated recombinant tissue plasminogen activator-thrombolysis is observed in humans [172]. Likewise, microbubble-enhanced focused ultrasound (FUS) is used to enhance the delivery of small-molecules of therapeutic agents into the brain for brain tumor treatment FUS-BBB opening. It shows significant permeability-enhancing effect on tumor peripheral drug distribution and exposure [171]. Hence to locate the opening in the BBB, pharmacodynamic analysis of magnetic resonance imaging-monitored focusing is used [171] (Figure 5).

Chemotherapy alone marginally improves the anti-tumor effect of patients with glioblastoma because the therapeutic dosage of many drugs is impeded by the blood-brain barrier (BBB) [175]. But chemotherapy of targeted liposomal platinum compounds with focused ultrasound increase the permeability functions of BBB [175] and could transfer higher doses of drug at the tumor sites. For example, administration of AP-1 liposomal cisplatin (lipoplatin) is followed by focused ultrasound (FUS)-induced BBB disruption increase the amount of drug delivered inside brain. No doubt GBM chemotherapy with AP-1 lipoplatin is followed by pulsed FUS exhibits a modest improvement of tumor growth in the brain compared to the group treated with lipoplatin alone. Lipoplatin is used in treatment of malignancies [175]. High-intensity focused ultrasound (HIFU) pulse trains can be frequency modulated to produce a radiation pressure having a similar form. But HIFU shows bio-effect and cause mild traumatic brain injuries in animals [176]. High intensity focused ultrasound is used to study of mild traumatic brain injury [176]. 1.5-MHz HIFU pulse trains of 1-ms duration are to intact skulls of mice *in vivo* and resulted in blood-brain barrier disruption and immune responses (astrocyte reactivity and microglial activation).

Drug delivery is enhanced by means of intravenous administration of boronophenylalanine (BPA) with blood-brain barrier disruption induced by focused ultrasound (FUS). FUS significantly enhances the tumor-to-normal brain drug ratio in the sonicated tumor and subsequently the efficacy of boron neutron capture therapy [177]. Similarly, Boron neutron capture therapy is used to enhance drug delivery and antitumor effect following blood-brain barrier disruption induced by focused ultrasound [177]. Interestingly, combined ultrasound-mediated BBB disruption may significantly increase the antineoplastic efficacy of liposomal doxorubicin in the brain [178]. Similar antitumor effects improve facilitation of liposomal doxorubicin after targeted blood-brain barrier disruption by MRI-guided focused ultrasound in rat glioma [178]. However, transcranial Doppler sonography, positron emission tomography and perfusion MRI are used also by applying wide-field low-frequency ultrasound (300 kHz). It helps improves cerebral hemodynamics in patients with cerebral small vessel disease [172]. Although, patient face excessive bleeding with low-frequency sonothrombolysis but primary blood-brain barrier disruption is easier than ultrasound [172]. Ultrasound at frequencies of 1.0 mcps

and 2.5 mcps can be focused to loosen the BBB at focal region. Metastasis in tissue under irradiation can be finished by increasing the ultrasonic intensity and duration of exposure [172]. But fiber tracts of the central nervous system are more vulnerable to ultrasonic irradiation than aggregates of cell nuclei or vascular structures and destructive action of the ultrasound. It results in mechanical strain and rise in temperature at the focus of the beam that hits at blood-brain barrier mainly at target sites [174].

6.5. Effect of Photoradiation

Interstitial photoradiation causes significant brain damage, disruption of blood brain barrier (BBB). It generates brain edema in LIA for laser power outputs in excess of 100 mW from the diffusion tip [179]. Photoradiation is localized to limit brain tumors by using 99MTc-GH imaging BBB in patients. Patient recovers partially due to combined treatment of operated brain tumors, by using radiotherapy preceded by chemotherapy. Although, it enhances the destruction of the BBB but facilitate the incorporation of drugs into the tumor. A 20-30 Gy dose of radition is provided to open the blood-brain barrier (BBB) and increase the drug permeability by altering the regional blood flow [180]. Thus, influence of radiation on the blood-brain barrier increases with the optimum time of chemotherapy [180]. Similarly, ocal neodymium: yttrium-aluminum-garnet (Nd:YAG) laser irradiation causes cerebrovascular and metabolic effects on the rat brain [181]. Similarly, neodymium yttrium aluminum garment laser affect the cerebral blood vessel and blood brain barrier [182]. It alters the regional cerebral blood flow, cerebral protein synthesis, and blood-brain barrier permeability. Moreover, sequential functional changes occur after irradiation which pertains to morphological alterations, protein synthesis inhibition, vasogenic edema, central coagulation necrosis and persistent perifocal ischemia. Extent and severity of ischemia in a zone depends on extensive scattering of light within brain parenchyma that may associated with a high blood-to-brain absorption ratio which selectively affects blood vessels outside the irradiation focus [182]. Similarly, a dose of 30 Gy in irradiated animals showed significant morphological changes with extensive necrosis in the fimbria, hemorrhages in the hippocampus, thalamus, and fimbria [182] which later on extend into the internal capsule, optic nerve, hippocampus, and thalamus. 1.44-microns Nd:YAG laser is useful in surgery in combination to photo-evaporative CO2 laser [183]. More specifically, rats in the 30 Gy treatment group showed stereotypic and ambulatory behavioral hyperactivity 32 weeks after irradiation [183]. Animals showed variable experimental decreased growth rate and urine osmolalities. Fetal hypothalamic transplants into brain irradiated rats showed graft morphometry and host behavioral responses [184] (Figure 5).

6.6. Effect of X-rays

X-ray irradiation causes tissue damage in the brain of adult rats and generates middle cerebral artery (MCA) thrombosis on the integrity of the blood-brain barrier (BBB). X-rays (dose of 0.5 Gy) generate an acute effect on vessel diameter in cultured endothelial cells and alter permeability functions of blood brain barrier. Chronic exposure of X-rays affects vascular architecture including telangiectasia and decrease in vascular density. An increase in charged particle exposure of 15 and 30 Gy, radiation causes significant changes in the blood brain barrier and vascular changes in the central nervous system. Likewise, chronic exposure to alpha particles causes vascular damage in compact bone resulting in bone infarcts, and collagen of the papillary dermis mainly microvasculature [185]. By using HRP within arterioles, venules and capillaries this radiation imposed effects can be reduced. Although, bilateral HRP leakage occured after MCA stenosis or femoral artery occlusion in patient [186]. At these sites, the vascular endothelium contained HRP-filled pinocytotic vesicles and tubular profiles. Endothelial-platelet interactions at the site of vascular injury may be responsible for releasing substances or neurohumoral factors which contribute to the acute opening of the BBB [186] (Figure 4).

X-irradiation affects pharmacokinetics of methotrexate in rats and alters the blood-brain barrier permeability [187]. But irradiation hardly shows any effect on the MTX concentrations in the plasma, heart and kidneys and does not affect MTX uptake and elimination. Contrary to this, the carbon dioxide laser causes lesser damage to the blood-brain barrier surrounding in corticotomy than surrounding conventional bipolar coagulation [31]. Similarly, kainic acid (KA) shows systemic action at 1 mg/kg and crosses the normal blood-brain barrier (BBB), but it does’nt generate observable pathophysiological effect related to human epilepsy [188]. Permanent insertion of 5- to 7-mCi seeds of iodine-125 (125I) for interstitial radiation shows an increase in permeability through BBB but it imposes cerebral edema [23].

6.7. Radiation-protective Effects of Drugs

Radiation treatment causes unidirectional transport of drugs from blood-to-brain and blood-to-tumor [188]. Some drugs can remove radiation generated effects and reverse the physiological integrity of BBB. PPARs (Peroxisomal proliferator-activated receptors) assist in repairing of radiation induced injury [189]. Anti-inflammatory strategies are employed to modulate radiation-induced brain injury. Traditionally, PPARs (Peroxisomal proliferator-activated receptors) agonists are known to play a role in metabolism, by regulating the response to inflammation and oxidative injury. PPARs agonists cross the blood-brain barrier and confer neuroprotection in animal models of CNS disorders such as stroke, multiple sclerosis and Parkinson's disease [189]. These PPARs agonists are ligand-activated transcription factors that belong to the steroid/thyroid hormone nuclear receptor superfamily. Similarly, 5-hydroxytryptamine shows radiation-protective effects in CNS [190] while α-difluoromethylornithine (DFMO) does modification of 125I-induced brain injury [191]. Further, corticosteroids decrease the permeability of tumor capillaries to small hydrophilic molecules (including those of some chemotherapeutic agents) and steroid pretreatment prevents acute, potentially dangerous and increases in tumor capillary permeability following cranial irradiation (Figure 3).

For reduction of post-irradiation damage vasoactive [192] drugs like temozolomide (TMZ) and erlotinib (ETN) are administered. These drugs easily cross the blood-brain barrier and enhance median survival times in tumor patients [193]. Dipyridamole therapeutics increases blood flow and reduces thrombosis, delay and reduce the onset of ataxia. A low iron diet and desferrioxamine reduces reperfusion injury and ataxia. It helps in development and exacerbation of radiation damage to the spinal cord. Iopamidol, a new water soluble nonionic radiographic contrast medium is used to dilute radioactivation [194]. Such medium form vesicles (niosome) do entrapment, absorption and distribution of methotrexate in mice and increase sustaining potential in irradiated animals [195]. Dexamethasone reduces blood-brain barrier damage caused by acute hypertension in X-irradiated rabbits [196]. Similarly, antineoplastic agents are found helpful to reduce effect of ionizing radiation in human cancer patients [197].

Baicalin is one of the principal flavonoids isolated from the dried root of Scutellariae Baicalensis Georgi [198]. It is widely used as a traditional herbal medicine to suppress brain edema and reduce cerebral ischemic damage. Baicalin reduces the permeability of the blood-brain barrier during hypoxia *in vitro* by increasing the expression of tight junction proteins in brain microvascular endothelial cells. Bevacizumab is a monoclonal antibody, which neutralizes the effect of vascular endothelium growth factor (VEGF) allowing regression of tumor vessels and a decrease in the permeability of the blood-brain barrier in the patient from continuing. It is used to treat patients who had developed severe side effects, radiolesion, and perforated corneal ulcer [198]. Arginine-rich cell-penetrating peptide dramatically enhances AMO-mediated ATM aberrant splicing correction and enables delivery to brain and cerebellum [199]. Furthermore, multiple injections significantly increased uptake of drugs in all areas of the brain, notably in cerebellum and Purkinje cells, and showed no signs of toxicity. Therapeutic potential of (RXRRBR)(2)XB-AMOs in A-T and other neurogenetic disorders is highly remarkable [199]. Metalloporphyrin antioxidants are proved good radio-protectants for tumor treatment after cranial radiotherapy/radiosurgery applications. These drugs ameliorate normal tissue damage in rat brain [200]. Exogenous hypoxia was shown to promote the normalization of transport through the capillary wall as a result of the prevention of injury of the structure and metabolic processes in endothelial cells and basal membrane [89]. Nicaraven inhibit poly (ADP-ribose) polymerase activity by exhibiting protective effects in ionizing radiation- and ara-C-induced cell death [201]. Hence, preclinical and clinical evaluation of new drugs and agents are highly essential. Preclinical drug screening purposes heterotransplantation of specific human tumors yields a model with high validity for tumor markers and drug response. In addition, optimized preload leakage-correction methods are helpful to improve the diagnostic accuracy of dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in post-treatment gliomas [202]. Similarly, T2-weighted spin-echo MRI showed FMNPs penetratin the blood-brain-barrier (BBB) and were found distributed in various organs, including the liver, testis, spleen, lung and brain. Radiation effects on nitroxyl decay of a lipophilic spin probe in the head region [203].

7. Biomarkers for Radiation Injuries

Radiation theraputics is an emerging area of medicine and clinical science because of its important role in tumor and cancer treatment. Certain biomolecules level in body fluids are used to detect radiation induced injuries in patients. Radiation induces shift in substrate preferences from fatty acids to glucose, hence, it works as a metabolic marker. Both hematopoietic and gastrointestinal tract cells remain highly susceptible to radiation. Hence, epidermal growth factor receptor (EGFR) is over-expressed in nearly all cases of squamous cell carcinoma of the head and neck (SCCHN), and is an important driver of disease progression [204]. Thus, EGFR quantization is done to evaluate status of carcinoma and be useful in clinical benefit for SCCHN treatment and act as a molecural marker [204]. Irradiation of other nearby tissues like myocardium also faces severe damage which can induce serious health problems leading to the heart ischemia and heart failure. These structural damages can be used to establish morphological markers, while significant alterations in neural tissues biomolecules may develop as molecular markers for diagnosis of radiation realted injuries in experimental animals. Normally irradiated tissues exhibit lower expression of PPAR-alpha (Peroxisome Proliferator-activated Receptor alpha) than the control animals. Similar reports are available on *in vivo*, dacomitinib treatment which delays tumor growth. A decreasing phospho-EGFR and Ki-67 immunoexpression are emerging as biomarkers to be used for detection of radiation injuries [204,205]. has developed multiple blood biomarkers which can easily provide early-response assessment of radiation exposure using a murine (CD2F1, males) total-body irradiation (TBI) model exposed to ^{60}Co γ rays (0.6 Gy min^{-1}) over a broad dose range (0-14 Gy) and time points (4 h-5 d). These markers are highly useful in identifying injuries due to nuclear accidents/terrorist attacks which could expose large numbers of people to ionizing radiation. Dose-dependent changes in hematopoietic cytokines: Flt-3 ligand (Flt3L), interleukin 6 (IL-6), granulocyte colony stimulating factor (G-CSF), thrombopoietin (TPO), erythropoietin (EPO), and acute phase protein serum amyloid A (SAA) can serve as physiological markers. While dose-dependent changes in hemodynamic parameters mainly blood cell counts i.e. lymphocytes, neutrophils, platelets, and ratio of neutrophils to lymphocytes can provide initial information about radiation exposure and work as cellular markers. Protein coupled with peripheral blood cell counts can be used among irradiated and non irradiated successful groups irradiated to different doses these are considered to be as biochemical markers. Similarly, dynamic changes in the levels of SAA, IL-6, G-CSF, and Flt3L reflect the time course and severity of acute radiation syndrome (ARS) and may function as prognostic indicators of ARS outcome [205]. Plasma proteins level can be used for assessment of radiation exposure at an earlier stage and become a conventional biodosimetry to give early

diagnostic information to manage radiation casualty incidents effectively. Level of certain factor and plasma proteins can serve as immunological and inflammatory markers. It can assist in reducing mass-casualty radiological incidents [205].

7.1. Recovery from Radiation Exposure and Its Effects

Various physiological and biochemical reactions start in response to radation during recovery. These reactions remove off or minimize the effect of particulate radiation that comes into play whatever the agent that caused the damage. For example, when a chromosome is broken, its broken ends starts rejoining and reconstitutes the chromosome. Occasionally the broken ends may seal over before rejoining and leaving permanent chromosome damage. When two or more chromosomes are broken within the same cell, rejoining of inappropriate broken ends takes place. This leads to permanent chromosomal change of a different kind. Though repair of chromosomes takes place, but repair processes following radiation damage is not specific in respect to normal damage. These particular examples and others relating to DNA are important in practice only for very large exposures. Repair starts only in cells which are exposed to sub-lethal dose of radiation second damaged cells are replaced by new population of cells. Repair of a specific tissue may be carried out without complete replacement of all the cells of the tissue while healing may involve tissue atrophy and/or fibrosis and the irradiated tissue may be permanently scarred. But in heavy radiation no recovery is possible and most of the cells die due to combined reasons of physiology and biochemistry. Individual irradiated cells have the ability to repair themselves as long as the amount of intracellular damage does not exceed a threshold value. Among all irradiated cells, if a single cell remains scare off the radiation, it starts rapid divisions while nearby cells become abnormal and are replaced simultaneously after arrival of new population of cells. But it is true that among irradiated cells, those cells get survive in which either no radiation energy or a sub-lethal amount is deposited. In such cells restoration of physiological activities takes place after some time. Interestingly, this mechanism for recovery is more effective in cells which do not undergo active cell division, e.g., quiescent stem cells, than in cells undergoing active cell division. The basal cells of the intestinal crypts and the ordinary blast cells of the bone marrow remain quiescent and its full recovery from sub lethal radiation damage takes only a few hours.

Repopulation brought about by stem cell proliferation is an important recovery mechanism in both the bone marrow and the gastrointestinal tract. While after radiation exposure cell number gets reduced but stem cells divide normally in both these tissues, and replace damaged cells. More often, stem cell turnover is maintained to compensate for the normal continuously occurring removal of differentiated cells. Interestingly, cell division in stem cells gets accelerated by large doses of radiation which increases with the radiation dose applied on cell population. More often in bone marrow, large macrophage cells generate certain factors which stimulate or shut down the stem cells which act as progenitors of erythropoeitic, granulopoeitic, thrombopoietic lineage of cells. On the basis of concentration of factors secreted stem cells repopulate the tissue but as soon these activity get slow down, repopulation gets restarted. These factors also regulate cell cycle in exposed and unexposed cells which decide the recovery rate and cell proliferation in bone marrow and GI tract. In case of heavy exposure for longer duration repopulation is hampered in both the systems.For recovery from radiation generated effects equivalent dose formula should be applied to quantify recovery.When operating in fallout conditions lethal effects and dose response can be determined that can also quantify recovery period from accumulated radiation exposure. These can formulas can predict the levels of external exposure that could be tolerated from fallout fields. But war time exposure is exceptionally has no measures; these formulas can predict only lethality, not radiation sickness. Current equivalent dose formulas are applicable to a very small portion of a battlefield population, because they are valid only for external gamma doses received at low dose rates (Figure 5).

7.2. Precautionary Measures

For laboratory technicians, researchers and employers/ workers primary radiation safety measures and healthful workplace should provide. Radiation working groups should ensure engineering controls to minimize or eliminate potential radiation exposure. For this purpose a comprehensive training about the potentially hazardous working conditions, and institute medical surveillance programs should be provided to avoid radiation related risks. However, for minimizing the radiation spills and exposure from radiation-emitting equipments, these must be effectively shielded inside poly plastic thick shield or should be covered inside a radiation absorption chamber or bag. For laboratory and industrial workers radioactive protective clothing and eyewears should be provided. They should be knowledgeable about potential safety measures, health effects and dangers of radiation exposure. Every employee should know about first aid procedures and to hazard warning signs, labels, and the identification of restricted areas. Regular employees should pass through routine medical examinations to recognize physiological/biological effects resulting from occupational radio frequency radiation exposures. CAM therapies can be provided to alleviate side effects of radiation therapy including probiotics, psyllium, exercise, melatonin, honey, acupuncture, and calendula [206].

In homogeneous radiation with limited penetration is used in certain types of therapeutics. Same is experienced with exposure to solar particle events outside the protection of the Earth's magnetic field [169]. Both homogeneous and heterogenous radiation induces inflammation with resultant specific loss of regulatory T cells from the skin. This results in a hyper-responsive state with increased delayed type hypersensitivity *in vivo* and CD4+ T cell proliferation *in vitro* [169]. Solar ultraviolet (UV) radiation has deleterious effects on the skin, including sunburn, photoaging and cancer. These compounds protect molecular targets by scavenging reactive oxygen species, including excited singlet oxygen and triplet state molecules, and also modulate stress-

dependent signaling and/or suppress cellular and tissue responses like inflammation [207]. Ionizing radiation affects skin immune function and imposes adverse side effects [208]. There is a lack of lack of consistency in both the prevention and management of radiation-induced skin toxicity [208].

Hence, to overcome the problem of radiation induced effects hypofractionated stereotactic radiotherapy and partial-brain irradiation with hfSRT (Novalis System) is provided to small animals. Local radiotherapy with pharmaceuticals was also found superior to local radiotherapy alone because it preserves neurological functions [209]. Similarly, Eribulin treatment may be beneficial for breast cancer patients with brain metastases progressing after whole brain radiation therapy [76]. Reduction of radiation damage to the spinal cord is possible by post-irradiation administration of vasoactive drugs [191] such as temozolomide (TMZ) and erlotinib (ETN). These drugs easily cross the blood-brain barrier and enhance median survival times in tumor patients [192]. Anti-angiogenic agents, such as bevacizumab (BEV), can induce normalization of the blood brain barrier. 0-(beta-hydroxyethyl)-rutosides also show radiation-protective effects like anti-edema in the rat brain which is visualized in the terminal blood stream [112]. Severe perivascular cell alterations can be prevented by the pretreatment with HR. Hence, drugs which show anti-edematous effect and can finish radiogenic cell oedema of the perivascular neuropile and act as membrane protector should be preferred [112]. These are much advantageous to minimize radiation induced neuro-pathologic effects (Figure 5).

Table 2. Major side effects of radiation and morbidities observed after radiation therapy of tumor patients.

Therapy used	Radiation type	Dose	Effect	References
TM Radiation therapy	Gamma radiation (5 Gy	5 Gy	Human vasculature	[14]
			effect on leukocyte-endothelial interactions and astrogliosis	[70]
Radiotherapy	Gamma radiation	40 cGy, (111) In- BnDTPA-Tz)	For making selective permeabilization of the blood-brain barrier at sites of metastasis affects blood-cerebrospinal fluid and blood-brain barrier, induced a rapid and transient decrease in TEER	[43] [14]
Interstitial radiotherapy	125I	5- to 7-mCi	changes in BBB function	[36]
Radionucleides	Platinum drugs	platinum drug in a liposome in nM	morphological effects, localization of adhesion and cell junction proteins and permeability of molecules through the endothelial barrier	[40]
X- ray irradiation	X- ray	Roentgen rays	changes in the functional status of the hemato -encephalic barrier , affects vascular architecture including telangiectasia and decrease in vascular density	[70,169]
Therapeutic examination	Radioactive phosphorus	Roentgen rays	showed delayed effects	[83]
Whole-brain irradiation	Neutrons/ Gamma radiation	15 Gy	generate autoimmune encephalomyelitis and neuroimmune diseases	[9]
Ionizing irradiation-induced radical stress	X-rays	>40 Gy (4-krad) X-rays stalls	Ionizing irradiation-induced radical stress, meiotic chromosome movements by altering the actin cytoskeleton, cervical cancer	[134] [127]
			affect oogenesis in Drosophila	[133]
Photo radiation	UV and light beams/waves/photons	1.5-MHz HIFU	Affect sexual development of *Hypocrea jecorina*	[135]
Atom bomb fission	Radiation fall out		leukemogenic effects	
Iridium-192			interstitial microwave hyperthermia	
brachytherapy				
Radioisotpes	14C	5-10mCi	cerebral cortex, hypothalamus, cerebellum and medulla	[85]
Boron neutron capture therapy	Boronophenylalanine and Ultrasound	1.5-MHz HIFU	open blood brain barrier for drug delivery to brain, treat brain tumors to fasten the distribution and dynamics of small molecule	[156,157]
Focused ultrasound	Waves	liposomal platinum compounds nM	increase the permeability functions of BBB, used for treatment of malignancies	[160]
Boron neutron capture therapy	p-boronophenylalanine (BPA) or borocaptate sodium (BSH) are used as neutron capture agents	500 mg/kg	enhanced drug delivery and antitumor effect	[53]
Interstitial photoradiation causes		99MTc-GH imaging	generate brain edema	[163]
Focal neodymium:yttrium-aluminum-garnet	laser irradiation	lambda = 1060 nm 20 watt impacts	cerebrovascular and metabolic effects on the rat brain, severe ischemia, affect the cerebral blood vessel and blood brain barrier	[165,166]
Alpha particles	X-rays	0.5 Gy-2 Gy.	resulting in bone infarcts, and collagen of the papillary dermis mainly microvasculature	[169]
(125I) for Interstitial iodine radiation therapy	iodine-125	5- to 7-mCi	increase in permeability but imposes cerebral edema	[172]

Trans-endothelial electrical resistance

Hence, to replace harmful effects of radiation therapy cancer patients can utilize complementary and alternative medicine (CAM) or natural plant products can be provided for chemotherapeutics on the advice of good oncologist. These medicines do reduction in side effects faster than any other conventional treatment used [206]. Chocolate flavanols act as strong antioxidants and anti-inflammatory molecules that could play a role in preventing cutaneous UV damage [210]. High-flavanol chocolate (HFC) consumption reduce the skin sensitivity to UV radiation, measured [210]. Dietary antioxidants can also reduce the side effects of radiation therapy [211]. A number of efficient micronutrients are found capable of contributing to the prevention of UV damage in humans [207]. Micronutrients present in the diet such as carotenoids, vitamins E and C, and polyphenols contribute antioxidant defense and make endogenous photoprotection [207] (Table 2). A combination of vitamins E and C protects the skin against UV damage. It is suggested that daily consumption of dietary polyphenols may provide efficient protection against the harmful effects of solar UV radiation in humans. Furthermore, the use of these micronutrients in combination may provide an effective strategy for protecting human skin from damage by UV exposure [207]. *Nigella sativa* oil (NSO) and thymoquinone (TQ) shows antioxidant and radioprotective effects against ionizing radiation-induced cataracts in lens after total cranium irradiation (IR) of rats with a single dose of 5 gray (Gy) [212]. These release nitrosative stress in lens tissue in radiation-induced cataract in rat [212]. Baicalin is one of the principal flavonoids isolated from the dried root of Scutellariae Baicalensis Georgi that is widely used as a traditional herbal medicine to suppress brain edema and reduce cerebral ischemic damage. Baicalin reduces the permeability of the blood-brain barrier during hypoxia in vitro by increasing the expression of tight junction proteins in brain micro vascular endothelial cells. Sonic hedgehog, a secreted protein involved in cell proliferation and angiogenesis [167]. Moreover, Sonic Hedgehog transfected adipocyte derived stem cells may improve wound healing[167]. Inhalation of HCG (1.3% hydrogen + 20.8% oxygen + 77.9% nitrogen) prior to the irradiation significantly decreased the delay in wound healing compared with the control and post-inhalation of HCG groups. Therefore, radiation-induced skin injury can potentially be alleviated by the pre-inhalation of HCG [213]. It also heals impaired skin wounds in rats and finish radiation-induced skin injury [201]. Skin protects the body from radiation up to permissible exposure limit of natural or artificial radiation dose (Table 2). The skin serves multiple functions that are critical for life [169]. However, trolamine cream (Tc), is used for the treatment of radiation dermatitis in rats. It protects the cellular and subcellular structures of skin after irradiation [214].

Radionuclides encapsulated in a liposome reduce the neoplastic effect and toxicity [48]. However, for better therapeutics of tumor patients fine nanomaterials or nanoparticles are to be used to load drugs for improving the bioavailability of a gene or to generate drug delivery system [50]. Due to their biocompatibility nanoparticles do not produce adverse effects on human health and the environment, hence these are considered as much safer drug delivery vehicles. These are used to administer therapeutic drugs in the human body by using different routes. Both inhaled fluorescent magnetic nanoparticles [50] and silver nanoparticles (Ag-NPs) interact with the cerebral microvasculature induced blood-brain barrier inflammation and increased permeability in primary rat brain microvessel endothelial cells [51]. In addition, for recovery of patient's bio-leachers, extractors, solubilizers and anti-angiogenic and vasoactive drugs should be used. For better protection one should immediately avoid repetitive use of radiation or radiation devices in daily life. For primary protection shielding, solubilizers, anti-angiogenic agents and radio protective drugs should be used. These drugs can minimize the level of radiation and reduce toxic effects by promoting cell repairing and inducing regenerating system of the patient body. Undoubtedly, instant use of combination therapies, radiation and micro-particle loaded drugs, in liposomes prove more effective for tumor therapeutics. Further, a variety of recovery processes are to be known which can reduce radiation damage to a varying extent. In addition, systemic use of corticosteroids, hyperbaric oxygen therapy free-radical scavengers can be used for treatment of irradiated patients, especially in acute phases (Table 2).

8. Conclusion

This paper has reviewed recent information radiation induced acute effects on human body mainly on organs, tissues, cells and biomolecules. Present article explains pathophysiological effects of accidental and experimental ionizing radiation on blood-brain barrier (BBB), skin, eyes, blood cells, nerve cells and osteoblasts. Radiation irradiates neuro-sensory, integumentary, blood and immune cells, and evokes adaptive and humoral immune responses and even autoimmune disorders. There occurs a cumulative effect of sub-lethal dose of both diagnostic and therapeutic radiation. It affects germ cell and embryonic development, cause point mutations in healthy normal body cells. Conceptually, therapeutic methods which can easily solubilize particulate radiation and leaching out it from the body tissues of patients should be favored. For better recovery new therapeutic models based on integrative approach should discover novel drugs, genes, growth factors, metals, enzymes, proteins, and plant natural products that may become target molecules. These could start physiological and structural regeneration of membrane surfaces and can restore cell and tissue metabolism in radiation affected cells should be promoted for therapeutic use. In addition, potential anti-cancer agents should be favored for the treatment of cancer and tumor rather than using radiation alone. Further, promising candidate molecules which could induce regeneration and evoke immune-modulation in cells and tissues should be identified. It is also important to seek earlier diagnosis of radiation related injuries by exploring new biomarkers with potential therapeutic applications. No doubt such combination therapies can aptly finish brain metastasis can become landmark discovery in the field of cancer biology. It will require inter disciplinary researches mainly in the field of molecular biology, radiation biology, and clinical sciences to develop more

recent and non-invasive methods for tumor therapeutics. This innovative research area needs many conceptual improvements in radio-pharmacological therapies.

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Abbreviations

BBB=Blood brain barrier, CNS= Central nervous system, CSF= Cerebrospinal fluid, electromagnetic (EM) radiation, CNS = Central nervous system, TMZ= temozolomide, ETN = erlotinib, VEGF=vascular endothelial growth factor, WBRT= whole brain radiation therapy SRS = stereotactic radio-surgery, ETI =early transient incapacitation, TEER= trans-endothelial electrical resistance, SAR =Specific Absorption Rate (SAR), ALS =Amyotrophic Lateral Sclerosis, GBM=glioblastoma multiforme, BEV =bevacizumab (BEV), MRI =magnetic resonance imaging, EMF= electromagnetic frequency, TJ =tight junction, HIFU =high-intensity focused ultrasound, Tf-FMMs= transferring-conjugated flourescein loaded magnetic nano-particles.

Conflict of Interests

Author has no conflict of interests. The author alone is responsible for the content and writing of the paper.

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