Arab Journal of Nuclear Science and Applications, 46(1), (305-312) 2013

Protective Effect of *Carica papaya Linn* Against ?-Radiation-Induced Tissue Damage in Rats.

Osman, N. N. and Hamza, R. G.
Food Irradiation Research Dept., National Centre for Radiation Research and Technology (NCRRT), Atomic Energy Authority, Cairo, Egypt.

Received: 1/8/2012 **Accepted: 20/8/2012**

ABSTRACT

The present study was designed to determine the possible protective effects of the *Carica papaya* fruit aqueous extract (CP) against ?-radiation induced oxidative stress, biochemical and hematological alterations in male albino rats. *Papaya* (250mg/Kg BW /day) was given to male albino rats, via gavages for 6 days prior exposure to the 1st radiation fraction and the treatment was continued for 14 days after the 1st irradiation fraction till the end of the experiment (4 Gy / week up to 8 Gy total doses). The samples were taken from the blood and some organs, liver and kidney for the biochemical analysis. In the irradiated group, there were a significant decrease in RBCs, WBCs count and Hb content. Dramatic increments in the serum indices of liver (aspartate transaminase, alanine transaminase, alkaline phosphatase and bilirubin) and kidney (urea, uric acid and creatinine) functions were also recorded depicting a liver and kidney impairment state. Also, a significant increase in thiobarbituric acid reactive substances (TBARS) content and Xanthine oxidase (XO) activity in parallel to a significant decrease in the activity of xanthine dehydrogenase accompanied by a significant decrease in reduced glutathione content (GSH), superoxide dismutase (SOD), catalase (CAT) activities were recorded in both liver and kidney tissues compared to control group. Treatment with CP (250mg/kg) was found to offer significant protection against ?-radiation-induced toxicity in the tissues, which was evident by the improved status of most of the parameters investigated. These results suggest that CP could increase the antioxidant defense systems in the liver and kidney of irradiated animals, and may protect from adverse effects of whole body radiation.

Keywords: ***papaya, gamma-irradiation, oxidative stress, hematology, liver, kidney***

INTRODUCTION

Protecting living system from the onslaughts of ionizing radiation is of paramount importance in radiation biology. This has particular relevance in nuclear warfare, nuclear accident, and nuclear terrorism. Radiation protection is also important in the radiotherapy of cancer where normal cells are needed to be protected while cancer cells are exposed to high dose of radiation [(1)]. Whole body exposure to ionizing radiation may trigger in human and animals multiple organ dysfunctions directly related to an increase of cellular oxidative stress due to overproduction of reactive oxidative species from molecule ionization [(2,3)]. Ionizing radiation exposure involves the development of potentially serious health conditions. Acute effects mainly include hematopoietic cell loss, immune suppression, mucosal damage, and potential injury to liver and other tissues. Whole organ irradiation might lead to hepatocyte failure and radiation-induced liver disease such as hepatitis [(4)]. Extracts of several plants and a number of phytochemicals are reported to be modifiers of radiation effects in a variety of biological system. Human beings are consuming a large variety of phytochemicals, which could protect them from dangerous effects of radiation exposure.

Carica papaya L. (CP) belongs to the plant family *Caricaceae*. It is being cultivated widely for consumption as fresh fruit, dried and crystallised fruit as well as for use in drinks, jams and candies [5]. *Carica papaya* seed extracts have been shown to have several medicinal properties. Among these is the nephro-protective activity of the aqueous seed extract of the unripe mature fruits [6]. This may involve its antioxidant and/or oxidative free radical scavenging activities. The aqueous seed extract has also been implicated in the treatment of poison-related renal disorders [6]. The fruit and its seeds have antihelminthic and antiamoebic activities [7]. Crude extracts of *Carica papaya* seed have an antibacterial activity that inhibits the growth of both gram positive (*B cereus, Saureus and S faecalis*) and gram negative (*E coli, P vulgaris and S flexneri*) organisms [8], as well as anti-fertility effect on male rats, rabbits and monkeys [9]. In view of these considerations, the main objective of this study was to assess the role of CP in protecting the normal tissues from radiation-induced damage.

MATERIAL AND METHODS

Extraction of juice from fresh plant carica papaya (fruit):

Matured fresh *C. papaya* fruit was purchased from a local market. The fruit was peeled and the cream coloured seeds inside discarded, 100 g of the fruit was soaked in 100 ml of distilled water and incubated at room temperature for 72 h. The extract was sieved into a clean container and kept in the refrigerator until use [10].

Experimental Animal and their management

Male Albino rats (130–140 g) were purchased from the Egyptian Holding Company for Biological Products and Vaccines (Cairo, Egypt). The rats were allowed two weeks of acclimatization under standard laboratory conditions and maintained on standard rat feed and potable water *ad libitum*. All animal procedures were performed in accordance with the Ethics Committee of the National Research Center and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85–23, revised 1985).

Irradiation was performed through the use of a Canadian Gamma Cell-40 (137Cs) at the National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt. Rats of irradiated groups were exposed totally to gamma irradiation with a fractionated dose (4 Gy / week up 8 Gy) at a dose rate of Gamma cell (0.46 Gy/minute**).**

Animals were randomly divided into four groups each of 6 animals as follows. Control group: animals neither exposed to radiation nor treated with *papaya*. *Papaya* group (CP): animals received orally *papaya* aqueous extract (250 mg/Kg/day) during 20 successive days. Irradiation group (IRR): rats in this group were exposed to whole body gamma radiation with a fractionated dose (4 Gy /week up to 8 Gy ses). *Papaya* + irradiation group (CP+IRR): rats received *papaya* aqueous extract (250 mg/Kg/day) for 6 days before exposure to fractionated dose and within the period of fractionated irradiation (14 days).

Animals were sacrificed on the 15^{th} day post-irradiation. Blood was collected and liver and kidney tissues were removed for biochemical investigations. The activity of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) were measured as described by Reitman and Frankel [11] and John & Bauera [12] respectively. Total bilirubin was analyzed using the method reported by Malloy and Evelyn [13]. Uric acid, urea and creatinine were assayed in serum using kits according to the methods described by Fossati et al. [14], Patton and Crouch [15] and Jeffe [16], respectively. The extent of lipid peroxidation was assayed by the measurement of TBARS according to Yoshioka et al. [17]. Xanthine oxidase (XO) and Xanthine dehydrogenase (XDH) were determined according to Kaminski and Jewezska [18]. SOD and CAT activities were determined according to Minami and Yoshikawa [19] and Aebi [20], respectively. The content of GSH was determined according to Beutler et al. [21]. In all enzymatic determinants the proteins were evaluated according to Lowry *et al*. [22]. As well as, WBCs, RBCs and Hb content were estimated according to Dacie and Lewis [23].

The statistical package for social sciences SPSS/PC computer program was used for statistical analysis of the results. Data were analyzed using one-way analysis of variance (ANOVA) followed by Newman–Keuls post hoc test for multiple comparisons. The data were expressed as mean ±S.E. Differences were considered statistically significant at ($P < 0.05$).

RESULTS

Administration of *Carica papaya (CP)* to rats for a period of 20 days did not show significant changes in all the studied parameters, indicating that the extract did not affect the liver and kidney functions.

Serum biochemical parameters like AST, ALT, ALP and serum bilirubin in the irradiated group were significantly ($p < 0.05$) elevated as compared to those of normal control group. Treatment with *papaya* before and continued with ?- radiation exposure significantly ($p < 0.05$) reduced the AST, ALT, ALP and serum bilirubin levels towards the normal values (Table 1).

Table 1: Effect of CP treatment on AST, ALT and ALP activities and bilirubin level in irradiated rats.

Groups	AST (IU/L)	ALT (IU/L)	ALP (U/L)	Bilirubin (mg/dL)
control	24.15±0.74[c]	15.28±0.36[c]	88.52±1.27[c]	0.62±0.01[c]
CP	24.06±0.69[c]	15.27±0.30[c]	85.30±1.20[c]	0.60±0.02[c]
IRR.	51.11±0.85[a]	32.37±0.29[a]	151.29±1.31[a]	1.12±0.02[a]
CP+IRR	30.17±0.81[b]	18.68±0.28[b]	101.42±0.86[b]	0.71±0.02[b]

Values are expressed as means of 6 records ± Standard Error
Means with different superscripts are significantly different at the 0.05 level

Exposure of rats to ?-irradiation induced a significant increase in serum levels of urea, uric acid and creatinine when compared with normal control group. Administration of CP before irradiation showed a prophylactic effect since it significantly ($P < 0.05$) improved the elevations in urea, uric acid and creatinine serum levels induced by ? -irradiation as depicted in table 2.

Table 2: Effect of CP treatment on serum levels of urea, uric acid and creatinine in irradiated rats.

Groups	Urea (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)
control	24.96±0.68[c]	5.80±0.11[c]	1.11±0.05[c]
CP	24.64±0.48[c]	5.76±0.12[c]	1.07±0.02[c]
IRR.	50.14±0.35[a]	7.93±0.09[a]	1.87±0.08[a]
CP+IRR	33.15±0.27[b]	6.99±0.51[b]	2.41±0.09[b]

Legend as table 1

Table 3, shows that the exposure of rats to gamma radiation induced significant increase of TBARs levels and xanthine oxidase activitiy in parallel to significant decrease in the activity of xanthine dehydrogenase in hepatic and renal tissues compared to their corresponding values in the control group. Supplementation of rats with CP has significantly improved the xanthine oxidoreductase system in addition to a significant depression in TBARs levels compared to irradiated group.

Table 3: Effect of CP treatment on lipid peroxidation (TBARS), XO and XDH in liver and kidney tissues of irradiated rats.

Groups	TBARS (n mol/g tissue)		XO (mU/mg protein)		XDH (mU/ mg protein)	
	liver	kidney	liver	kidney	liver	kidney
control	113.10±2.43[c]	116.83±2.25[c]	2.18±0.05[c]	1.52±0.03[c]	3.11±0.05[a]	2.75±0.07[b]
CP	109.27±2.21[c]	114.42±1.65[c]	2.04±0.05[c]	1.50±0.03[c]	3.18±0.07[a]	2.69±0.06[b]
IRR.	165.40±2.21[a]	185.57±2.22[a]	3.51±0.08[a]	2.47±0.03[a]	1.65±0.07[c]	3.15±0.04[a]
CP+IRR	133.44±1.55[b]	148.78±1.58[b]	2.46±0.03[b]	1.66±0.06[b]	2.32±0.09[b]	2.00±0.02[c]

Legend as table 1

?- radiation induced significant decreases ($P < 0.05$) in GSH content, SOD and CAT activities of hepatic and renal tissues compared to their corresponding values in the control group (Table 4). Supplementation with CP has significantly ameliorated the antioxidant status of irradiated rats.

Table 4: Effect of CP pretreatment on SOD, CAT activities and GSH level in liver and kidney tissues of irradiated rats.

Groups	SOD (U/ mg protein)		CAT (U/ mg protein)		GSH (mg/g tissue)	
	liver	kidney	liver	kidney	liver	kidney
control	43.59±0.66[a]	29.81±0.44[a]	50.12±1.29[a]	35.73±0.22[a]	25.08±0.26[a]	21.14±0.09[a]
CP	44.17±0.27[a]	28.11±0.10[a]	48.20±0.58[a]	33.42±0.11[a]	25.13±0.26[a]	21.25±0.09[a]
IRR.	37.05±0.38[c]	18.32±0.13[c]	37.72±0.64[c]	19.52±0.14[c]	18.03±1.62[c]	12.72±0.09[c]
CP+IRR	40.79±0.16[b]	24.43±0.38[b]	44.72±0.12[b]	28.12±0.17[b]	21.94±0.13[b]	18.07±0.39[b]

Legend as table 1

Table 5 shows the RBC, WBC and Hb levels in the control and experimental rats. RBC and WBC counts were observed to be decreased in the radiation group; whereas administration of CP significantly improved the counts of RBC and WBC in rats when compared to the corresponding radiation group. Further, results of Hb content showed that there was a decrease in the level of Hb in irradiated group when compared to the control group. Administration of CP significantly improved the Hb levels in rats when compared to the irradiated group.

Table 5: Effect of CP on hematological changes in gamma)-irradiated peripheral blood of rats.

Groups	RBC (cells × 10^6/mm^3)	WBC (cells × 10^3/mm^3)	Hb (g/100 ml)
control	6.43±0.02[a]	12.55±0.02[a]	12.55±0.02[a]
CP	6.96±0.03[a]	12.58±0.02[a]	12.58±0.02[a]
IRR.	4.92±0.02[c]	9.47±0.02[c]	9.47±0.02[c]
CP+IRR	5.91±0.02[b]	11.67±0.03[b]	11.67±0.03[b]

Legend as table 1

DISCUSSION

Exposure to ionizing radiation whether occupational or during radiotherapy leads to serious systemic damage to various cellular and subcellular structures. Radiation exposure creates free radicals causing oxidative stress where antioxidant activity declines and lipid peroxidation increases [(24)]. It is well documented that dietary antioxidants play an important role in mitigating the damaging effects of oxidative stress on cells. The aim of the present study was to evaluate the effects of gamma irradiation on the antioxidant defence system and the radioprotection afforded by *papaya.*

Several enzymes of blood are considered as indicators of hepatic dysfunction and damage, and the leakage of hepatic enzymes such as AST, ALT and ALP into blood are routinely used as a reliable biochemical index for hepatocellular damage [(25)]. It was also found that hepato-cellular damage exhibited good correlation with the enzyme leakage to bloodstream [(26)]. In the present findings, ?-radiation caused a significant increase in the activities of AST, ALT and ALP (Table 1). These results are in accordance with other studies [(27, 28)]. The excessive production of free radicals and lipid peroxides might have caused the leakage of cytosolic enzymes such as aminotransferases (AST and ALT), and ALP [(29)].

In the present investigation, the increase in serum bilirubin concentrations in irradiated rats was observed. Raise in bilirubin level can be either due to increased (RBCs) and/or haemoglobin breakdown evidenced form the haematological alterations, or due to hepatic damage evidenced from the anomalous serum biochemistry. It was found that increase in serum bilirubin is associated with free radical production induced hepatic damage [(30)]. The restoration of AST, ALT, ALP and bilirubin levels to their respective normal level was observed in the CP treated group. This is consistent with previous report of Sadeque and Begum [(31)], who observed that the aqueous and ethanol extracts of *C.papaya* decreased the carbon tetrachloride, induced elevated levels of the enzymes like serum ALT, AST and ALP which were statistically significant compared to control group. This finding may indicate the dominant antioxidant effect of vitamin C which is richly contained in *C. papaya* [(31)]. As a measure of renal function status, serum urea, uric acid and creatinine are often regarded as reliable markers [(32)]. Thus, elevations in the serum concentrations of these markers are indicative of renal injury [(32)]. Elevated uric acid, urea and creatinine levels were observed in rats exposed to gamma radiation (Table 3). These results came similar to previous investigations by Konnova et al. [(33)] and Abou-Safi [(34)]. These increments could be considered as a reflection of deteriorating renal performance [(35)] due to the ammonia formed by deamination of amino acids in the liver which converted to urea [(36)] or to increased breakdown of nucleic acids [(37)]. Since irradiation may cause breaking of DNA molecules and destruction of their bases (the purines) which may be catabolized into uric acid [(36)]. As creatinine is formed largely in muscles and occurs freely in blood plasma and urine, its increased levels in plasma serve as an index of renal function impairment [(38)].

In the present study, the nephroprotective effect of the aqueous extract of *Carica papaya* was observed in gamma radiation induced acute nephrotoxic rats. The possible protective effect of the extract is mediated through antioxidant and/or free radical scavenging activities due to the high concentration of flavonoids and alkaloids they contain [(39, 40)]. In addition, papaya has been reported to contain flavonoids, alkaloids, saponins and other active phytocomponents [(41)]. Adeneye et al, [(42)] revealed that hot infusion of *Carica papaya* seeds is used in the treatment of poison related liver and renal diseases. Also, Olagunju et al., [(6)] reported the nephroprotective activity of the water extract of the plant seeds in acute model of CCl_4 renal injured rats. Lipid peroxidation is considered as a molecular mechanism of oxidation of cellular lipid based macromolecules. Overproduction of ROS enhances the lipid peroxidation and subsequently increases the lipid peroxidation products like malondialdehyde (MDA) and other TBARS levels which lead to degradation of cellular macromolecules [(43)]. Increased TBARS is regarded as a biomarker of enhanced lipid peroxidation [(44)]. A significant increase ($p < 0.05$) in the level of TBARS associated with the alteration of XOR system and conversion of XDH into XO activity (Table 3). The results are compatible with previous findings that ionizing radiation induces the conversion of XDH into XO [(45)]. The enhanced specific XO activity induces oxidative stress whereby the excess of free radicals interact with various components of the cell and resulted in elevation of oxidative products.

In the present study, the significant increase of oxidative biomarkers was associated to a significant decrease ($p < 0.05$) in the activity of SOD and CAT, and GSH content (Table 4) in liver and renal tissues of irradiated rats. In agreement with these results, Jagetia [(46)] and Mansour and Hafez,

[28] recorded a significant depletion in the antioxidant system accompanied by enhancement of lipid peroxides after whole body gamma-irradiation. The elevated level of TBARS could be attributed to the peroxidation of membranes lipid resulted in cellular structure modifications and oxygen radicals-mediated tissue damage [47]. The significant decrease ($p < 0.05$) in the activity of SOD and CAT might also be attributed to the excess of ROS, which interacts with the enzyme molecules causing their denaturation and partial inactivation [48]. The depletion in GSH may be due to its reaction with free radicals resulting in the formation of thiyl radicals that associate to produce oxidized glutathione (GSSG) [49].

In the current study, the oral administration of papaya has reduced oxidative stress. The data obtained revealed a significant reduction ($p < 0.05$) in the activity of XO and the level of TBARS (Table 3) with concomitant significant increase ($p < 0.05$) in the activity of XDH, SOD and CAT, and in the content of GSH (Table 4), in comparison with their corresponding values in irradiated rats. These results come in accordance with Sadek [50], who reported that administration of CP aqueous extract significantly ameliorated the increased levels of MDA and decline of GSH, SOD and CAT activity in the stomach, liver and kidney tissues caused by acrylamide toxicity. This is concurs also with other reports which showed that, *Carica papaya* contains antioxidant phytochemicals, such as vitamin C, beta-carotene, lycopene and vitamin E, that all of which act as antioxidant and subsequently decrease the consumption of these antioxidant enzymes to combat oxidative stress [51-55]. In a small double-blind, placebo controlled study, a fermented extract of *Carica papaya* was administered to elderly patients without major diseases, the fermented *Carica papaya* preparation supplemented group showed a significant enhancement of the individual's antioxidant defense system [56, 57].

Data of the present study have indicated that whole body ?-irradiation resulted in disorders in the haematological constituents as manifested by a significant decrease in the number of WBCs, RBCs and haemoglobin content (Table 5), which may be due to alteration in bone marrow as well as haemopoietic system of the animals. Similar observations were obtained by Dixit et al., [58]. Whole-body gamma-irradiation induced direct destruction of mature circulating cells, loss of cells from the circulation by hemorrhage, or leakage through capillary walls and reduced cell production [59]. The decrease in the values of hematological parameters following radiation exposure may be assigned to direct damage caused by a lethal dose of radiation [60]. The cellular elements of the blood are particularly sensitive to oxidative stress because their plasma membranes contain a high percentage of polyunsaturated fatty acids (PUFA) [61]. Therefore the decrease in white blood cells differential count recorded in the irradiated rats might be the consequence of radiation-induced lipid peroxidation and damage of their cell membranes. The decrease in hemoglobin content could be attributed to the decline in the number of red blood cells [62]. Whereas, administration of CP significantly improved the counts of WBCs and RBCs and Hb content in rat when compared to the corresponding radiation group. Oladunmoye and Osho [63] suggested that papaya possesses protective action on the haemopoitic system. This probably might have been implicated by the presence of flavonoids in CP.

CONCLUSION

It is concluded that papaya improve the antioxidants defense system by enhancing the activity of antioxidant enzymes (SOD and CAT), reducing of lipid peroxide contents as well as its hepato- and renal protection against bad effects of ?-irradiation. It is therefore suggested that papaya may find better prospects as antioxidant and radioprotector medicinal plant.

REFRENCES

1- Sandeep, D. and Nair, C. K. Exper. .Toxico. Patho.; 64, 57– 64 (2012).
2- Mettler, F.A. and Voelz, G.L. N. Engl. J. Med. ; 346, 1554–1561 (2002).
3- Coleman, C.N., Blakely, W.F., Fike, J.R., MacVittie, T.J., Metting, N.F., Mitchell, J.B., Moulder, J.E., Preston, R.J., Seed, T., Stone, H.B., Tofilon, P.J.and Wong, R.S. Radiat. Res.; 159, 812–834 (2003).
4- Khozouz, R.F., Huq, S.Z. and Perry, M.C. J. Clin.Oncol.; 26, 4844–4845 (2008).
5- Villegas, V. N. The Netherlands; 1, 447 (1997).
6- Olagunju, J. A., Adeneye, A. A., Fagbounka, B. S., Bisuga, N. A., Ketiku, A. O., Benebo, A.S., Olufowobi, O. M., Adeoye, A. G., Alimi, M. A. and Adeleke, A. G. Bio. and Med.; 1(1), 11-19 (2009).
7- Okeniyi, J.A., Ogunlesi, T.A., Oyelami, O.A. and Adeyemi, L.A., J. Med. Food; 10 (1), 194-196 (2007).
8- Dawkins, G., Hewitt, H., Wint, Y., Obiefuna, P.C. and Wint, B. West Indian Med. J.; 52 (4), 290-292 (2003).
9- Lohiya, N.K., Manivannan, B., Goyal, S. and Ansari, A.S., Asian J. Androl.; 10, 298-306 (2008).
10- Oduola, T., Adeniyi, F. A. A., Ogunyemi, E. O., Bello, I. S., Idowu, T. O. and Subair, H. G. J.Med. Plants Res.; 1 (1), 001-004 (2007).
11- Reitman, S. and Frankel, S. Am. J. Clin. Pathol.; 28, 56 (1957).
12- John, D. and Bauer, M. C.V. Mosby Co., USA, 9th ed.; 580-581 (1982).
13- Malloy, H.T. and Evelyn, K. A. J. Biol. Chem.; 2, 119-481 (1937).
14- Fossati L, and Berti, G. Clin. Chem.; 26 (2), 227–231 (1980).
15- Patton C, and Crouch, S. Anal.Chem.; 49, 464–469 (1977).
16- Jeffe, M. Z. Phys. Chem.; 10, 391-400 (1886).
17-Yoshioka, T., Kawada K, S. T. and Mori, M. Am. J. Obstet Gynecol.; 135, 372–376 (1979) .
18- Kaminski,Z. W. and Jewezska, M. M. Biochem. J.; 181, 177–182 (1979).
19- Minami, M. and Yoshikawa, H. Clin. Chim.Acta.; 92, 37–42 (1979).
20- Aebi, H. Methods Enzymol.; 105, 121–126 (1984).
21- Beutler, E., Duron, O. and Kelly, B. M. Lab. Clin. Med.; 61(5), 882–888 (1963).
22- Lowry,O.H., Rosenbrough, N.J., Far, A.L and Randel, R.J. J .Biol. Chem.; 193, 265-275 (1951).
23- Dacie, S.T. and Lewis, S.M. 7th ed. Churchill, Levingston. Medical Division of Longman Group UK Ltd (1991).
24- Nordberg, J. and Arner, E. Reactive oxygen species, antioxidants and mammalian thioredoxin system. Free Radic. Biol. Med.; 31, 1287 (2001).
25- Haldar, P.K., Adhikari, S., Bera, S., Bhattacharya, S., Panda, S.P. and Kandar, C.C. Ind. J. Pharm. Edu. Res.; 45, 108–113 (2011).
26- Awad, M.E., Abdel-Rahman, M.S. and Hassan, S.A. Toxicol.; 12, 699–704 (1998).
27- El-Missiry, M.A., Fayed, T.A., El-Sawy, M.R. and El-Sayed, A.A. Ecotoxicol. Environ. Saf.; 66 (2), 278–286 (2007).
28- Mansour, H.H. and Hafez, H.F., Ecotoxicol. Environ. Saf.; 80, 14-9 (2012).
29- Cromheecke, M., Konings, A.W., Szabo, B.G. and Hoekstra, H.J. Hepatogas- troenterology; 47, 1732–1740 (2000).
30- Thomas, W., Sedlak, M.D., Solomon, H. and Snyder, M.D. Pediatrics; 113, 1776–1782 (2004).
31- Sadeque, Md. Z. and Begum, Z. A. Bangladesh J. Phar.; l(5), 48-50 (2010).
32- Adelman, R. D., Spangler, W.L., Beasom, F., Ishizaki, G. and Conzelman, G. M. J. Antimicrobial Chemotherapy; 7(4), 431 – 440 (1981).
33-Konnova, l., Konnov, B. and Komar, V. Radiobiologya; 31(3), 410 (1991).
34- Abou-Safi, H., M. Egypt. J. Med. Sci;. 19 (1), 157 (1998).
35- Geraci, J. P.; Jackson, K. L.; Mariano, M. S. and Michieli, B. M. Rad. Res.; 112, 95 (1990).
36. Ganong, W. 19th ed., Appleton & Lange, California, USA; Chap. 17 (1999).

37- Yarmonenko, S. P. In: "Radiobiology of humans and animals"; Mir Publishers, Moscow; (1988).
38- Farag, M. H. Egypt. J. Rad. Sci. Applic.; 7 (1), 99 (1994).
39- Miller, N. J and Rice-Evans, C. A. Food Chem.; 60, 331 – 337 (1997).
40- Adeneye, A. A. and Benebo, A. S. J. Ethnopharmacology; 188, 318-323 (2008).
41- Adeneye, A. A. and Olagunju, J. A. Bio. Med.; 1(1),1-10 (2009).
42- Adeneye, A. A., Olagunju, J. A., Banjo, A. A. F., Abdul,S.F., Sanusi, O.A., Sanni, O. O., Osarodion, B. A. and Shonoiki, O. E. Int. J. Appl. Res. in Natural Products; 2(2), 19-32 (2009).
43- Das, A.K., Dewanjee, S., Sahu, R., Dua, T.K., Gangopadhyay, M. and Sinha, M.K. Environ. Toxicol. Pharmacol.; 29, 64–69 (2010).
??- Bhattacharya, S., Prasanna, A., Majumdar, P., Kumar, R.B.S. and Haldar, P.K. Pharm. Biol.; 49, 927–935 (2011).
45- Srivastava, M., Chandra, D. and Kale, R. K. Radiat Res. Mar.; 157(3), 290-7 (2002).
46- Jagetia, G.C. J. Clin. Biochem. Nutr.; 40, 74–81 (2007).
47- Mansour, H.H., Hafez, H.F., Fahmy, N.M. and Hanafi, N. sŽĐSGwW$A?wAĐŽ u???? ;??? ???–??? ;?????.
48- Kregel, K.C. and Zhang, H. J. Am. J. Physiol. Regul. Integr. Comp. Physiol.; 292, 18–36 (2007) .
49- Verma, S., Gupta, M. L. , Dutta, A ., Sankhwar, S., Sandeep K. S.and Flora, S.J.S. Oxidative Medicine and Cellular Longevity; 1, 44-52 (2010).
50- Sadek, K. M. Nature and Science; 10(3), 16-22 (2012).
51. Anuar,N.S., Zahari, S.S., Taib, I.A. and Rahman, M.T. Food Chem Toxicol.; 46(7), 2384-2389 (2008).
52- Amer, J., Goldfarb, A., Rachmilewitz, E.A. and Fibach, E. Phytother. Res.; 22(6), 820-828 (2008).
53- Looze, Y., Boussard, P., Huet, J., Vandenbussche, G.,Raussens, V. and Wintjens, R. Phytochemistry.; 70(8), 970-978 (2009).
54- Azarkan, M., Wintjens, R. and Looze, Y. Phytochemistry.; 65(5), 525-534 (2004).
55- Gouado, I., Schweigert, F.J., Ejoh, R. A., Tchouanguep,M. F. and Camp, J.V. Eur. J. Clin. Nutr.; 61(10), 1180-1188 (2007).
56- Marotta, F., Weksler, M., Naito, Y., Yoshida, C., Yoshioka, M. and Marandola, P. Ann. N. Y. Acad. Sci.; 1067, 400-407 (2006).
57- Osato, J.A., Santiago, L.A., Mori, A. and Horitsu, H., Magn. Reson. Med.; 6, 306–308 (1995).
58- Dixita, A. K., Bhatnagara, D., Kumarb, V., Chawlac, D., Fakhruddinc, K. and Bhatnagar, D. J. functional foods; 4, 197-206 (2012).
59- Casarett, A. P., editor. Prentice. Hall Inc.; 158–159 (1968) .
60- Heda, G.L. and Bhatia, A. L. Proc. Asian Reg. Conf. Med. Phys.; 390 (1986).
61- Chew, B. P. and Park, J. S. J. Nutr.; 134, 257S–261S (2004).
62- Malhotra, N. and Srivastava, P.N. Radiobiol. Radiother.; 19, 347–350 (1978).
63- Oladunmoye, M.K. and Osho, I.B. J. Plant Scie.; 2: 447-452 (2007).