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RESEARCH PAPER

Nanocurcumin as a radioprotective agent against radiation-induced mortality in mice

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ABSTRACT

Objective(s): Curcumin, a natural plant product, is commonly known as wonder drug of life, but the poor bioavailability of its free form has hindered its clinical development. The aim of the present study was to investigate the radioprotective effect of nanocurcumin on survival of mice under whole body X-ray irradiation.

Materials and Methods: The Naval Medical Research Institute (NMRI) mice randomly assigned to separate groups and received nanocurcumin via oral gavage at different time points related to irradiation. The survival of mice was evaluated daily for 30 days post-irradiation and finally, the LD50/30 was calculated using Probit analysis. The 30-day survival curve was plotted using the Kaplan-Meier survival curve and the median survival of different subgroups was compared using log-rank test. The P-values less than 0.05 were considered significant.

Results: Our results showed that the administration of oral nanocurcumin could effectively reduce the mortality rate in the irradiated mice. Five days pretreatment with nanocurcumin (4 mg/kg/day) induced maximum radioprotective effect. The LD50/30 was 7.18 Gray (Gy) (95% confidence interval [CI]: 6.59-7.77) and 8.78 Gy (95% CI: 8.14-9.50) for irradiation-only and the optimum nanocurcumin group (pre-irradiation group), respectively (dose reduction factor [DRF] = 1.22). Continued administration of nanocurcumin up to seven days post-irradiation resulted in no further radioprotection.

Conclusions: The results obtained in this study confirmed the efficacy of nanocurcumin as a radioprotective agent against radiation-induced mortality in mice. The specific characteristics of nanocurcumin, such as non-toxicity, edibility, availability, make this phytochemical as a potential radioprotective agent in the radiotherapy setting and radiation accidents. Further clinical studies are highly recommended.

Keywords: *Herbal radioprotector, Mice survival, Nanocurcumin, Whole-body irradiation*

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INTRODUCTION

Curcumin, a bioactive and non-toxic phytochemical, has long been of interest to various scientists due to multiple pharmacological functions such as antioxidant, anti-inflammatory, anticancer, immunomodulatory, and radiomodulatory features [1-4]. The development of herbal radiomodulators is of paramount importance because of its lower toxicity compared to chemical drugs [5-7]. The radioprotective properties of herbal and natural antioxidants, such as curcumin, have been shown in many studies [8, 9]. Dual function of curcumin as a radioprotector in a healthy tissue and a radiosensitizer in a tumor has led to the development of many promising research at different levels from cell to human [3, 10, 11].

The main barrier for application of curcumin in the clinic is its poor bioavailability due to

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low absorption in the digestive system and rapid metabolism [12, 13]. Recent promising studies have shown that the use of curcumin nanoformulations can lead to improved solubility, absorption capability, and bioavailability [13-16].

This study determined the 30-day survival of mice under whole body X-ray irradiation after administration of nanocurcumin at different time points related to irradiation to evaluate the radioprotective effect of nanocurcumin.

MATERIALS AND METHODS

Animals and materials

In this experimental study, 190 adult male NMRI mice with an approximate age of six to eight weeks and a weight range of 25-30 g were provided from the Pasteur Institute, Tehran, Iran. The mice randomly assigned to separate groups within subgroups of 10. All animal experiments were conducted in accordance with international guidelines, regulations enforced by the institutional review board, and the NIH guide for the care and use of laboratory animals [17]. The animals were kept in an animal lab at the Iran University of Medical Sciences for adaptation to the environment for 24 hours in a cage without medication only by taking water and food under standard conditions. The animals were placed under 12:12 light/dark cycle at 25±2°C. The nanocurcumin (SinaCurcumin®) was prepared from Exir Nano Sina Company (Tehran, Iran). The drugs were dissolved in distilled water and diluted to desired concentrations. Then, different concentrations of the drugs were administered to mice (0.2 ml/mouse, by oral *gavage*, once daily) pre- and/or post-irradiation. In the pre-irradiation groups, the oral administration included taking drug daily for 5 days before up to 2 hr pre-irradiation. In post-irradiation group, drug was orally administered daily on the day after irradiation up to 7 days later. In pre- and post-irradiation groups, nanocurcumin was administered before and after irradiation on the basis of both mentioned protocols.

To obtain the $LD_{50/30}$ for the irradiation-only group, a total of 50 mice within subgroups of 10 were exposed to X-ray alone without nanocurcumin and received the irradiation doses of 5, 6, 7, 8, and 9 Gy. In addition, 20 non-irradiated mice as control group received either 2 mg/kg or 4 mg/kg of nanocurcumin for 13 days. The $LD_{50/30}$ was determined for different modes of nanocurcumin administration on 120 mice divided into 4 following groups: 1) Nanocurcumin 4 mg/kg pre-irradiation; 2) Nanocurcumin 4 mg/kg post-irradiation; 3) Nanocurcumin 4 mg/kg pre- and post-irradiation; 4) Nanocurcumin 2 mg/kg pre- and post-irradiation. Each group was exposed to the irradiation doses of 7, 8 and 9 Gy within the subgroups of 10.

Prescribed amounts of 2 and 4 mg/kg as nanocurcumin doses were designated based on the manufacturer's recommendation.

X-ray irradiation and mortality assessment

In this study, the linear accelerator (Elekta Compact) with 6-MeV energy was used to expose the mice. The irradiation field was 35×35 cm^2. The mice were exposed to different doses of radiation with a source to sample distance (SSD) of 100 cm. The dose rate was 200 cGy/min. After exposing, the mice were housed under the same conditions to determine the 30-day survival rate. For this purpose, the lethality of mice was recorded for 30 days after exposure.

Dose reduction factor (DRF) calculation

For determination of the DRF as the ratio of radioprotection, the groups with and without receiving drug were exposed to different irradiation doses as mentioned and $LD_{50/30}$ was calculated for various treatment groups. The DRF of each treatment group was obtained by dividing $LD_{50/30}$ of that group by $LD_{50/30}$ of the irradiated group without drug as follows [18-20]:

DRF= (LD50/30 of drug groups)/(LD50/30 of the irradiation only group).

Statistical analysis

The $LD_{50/30}$ of different treatmnet groups and irradiation-only group was calculated by the Probit test and then 95% confidence interval (CI) was obtained for each one. The median survival of different subgroups was compared using log-rank test. The *P*-values less than 0.05 were considered significant. In addition, the 30-day survival curve was plotted using the Kaplan-Meier survival curve. The statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

The results in irradiation-only subgroups showed 100% survival for the mice exposed to 5Gy irradiation and 100% mortality for the mice

Table 1. The survival of different treatment subgroups

Group	Median survival, Day	30-day survival rate, %	*P*-Value compared to control	*P*-Value compared to irradiation-only
Control (0 Gy)	30	100		.067
7 Gy irradiation				
Irradiation-only	30	70	.067	
Nanocurcumin 4mg/kg Pre-irradiation	30	100	>.999	.067
Nanocurcumin 4 mg/kg post-irradiation	30	100	>.999	.067
Nanocurcumin 4 mg/kg Pre- and post-irradiation	30	80	.146	.546
Nanocurcumin 2mg/kg Pre- and post-irradiation	30	80	.146	.546
8 Gy irradiation				
Irradiation-only	16.5	10	< .001	
Nanocurcumin 4 mg/kg Pre-irradiation	30	90	.317	.001
Nanocurcumin 4 mg/kg post-irradiation	13.5	20	< .001	.579
Nanocurcumin 4 mg/kg Pre- and post-irradiation	16	40	.004	.541
Nanocurcumin 2 mg/kg Pre- and post-irradiation	16.5	40	.004	.290
9 Gy irradiation				
Irradiation- only	5	0	< .001	
Nanocurcumin 4 mg/kg Pre-irradiation	18	30	.001	< .001
Nanocurcumin 4 mg/kg post-irradiation	14	0	< .001	< .001
Nanocurcumin 4 mg/kg Pre- and post-irradiation	12	0	< .001	< .001
Nanocurcumin 2 mg/kg Pre- and post-irradiation	16	40	.004	< .001

exposed to 9Gy irradiation. There was no significant difference in the median 30-day survival between the mice exposed to 5, 6, and 7 Gy irradiation and non-irradiated control group (p>0.05). The median survival of the mice exposed to 8 and 9 Gy showed a significant difference with the median survival in the control group (p<0.001). The Kaplan-Meier curve for the irradiation-only mice is shown in Fig 1.

The 30-day survival of different treatment groups

The median survival and the 30-day survival rate of the different treatment subgroups compared to corresponding irradiation-only subgroups and control mice are shown in Table 1. The treatment subgroups exposed to 7Gy irradiation showed no significant difference in the survival rate comparedwith both the corresponding irradiation-

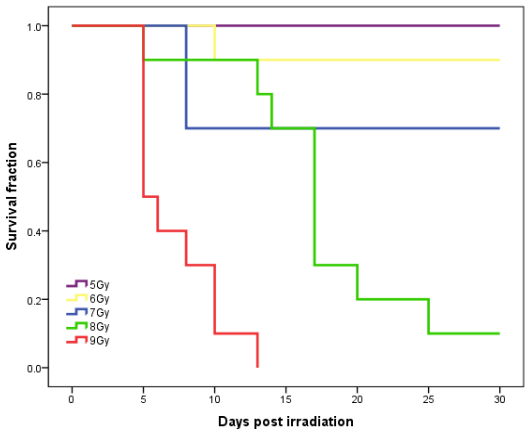

Fig 1. Kaplan-Meier curve for the irradiated-only mice

only subgroup and the non-exposed control group (Table 1).

The 30-day survival rate of the mice in the subgroups exposed to 8Gy irradiation varied from 20% in the subgroup of nanocurcumin 4 mg/kg post-irradiation up to 90% in the subgroup of nanocurcumin 4 mg/kg pre-irradiation. The Kaplan-Meier curve for the subgroups exposed to 8Gy irradiation is shown in Fig 2. Among the mice exposed to 8Gy irradiation, only the subgroup of nanocurcumin 4 mg/kg pre-irradiation showed a significant difference in the mean survival compared to the corresponding irradiation-only subgroup (Table 1).

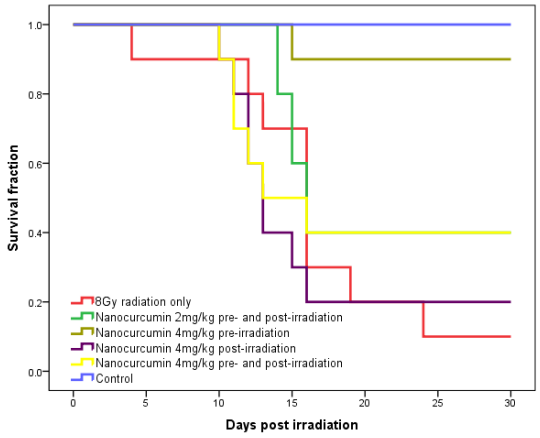

Fig 2. Kaplan-Meier curve for the subgroups exposed to 8Gy radiation

In addition, the median survival difference was significant between the pre-irradiation subgroup and other treatment subgroups exposed to 8Gy irradiation (p<0.05). As shown in Table 1, there is no statistically significant difference between the survival of mice in pre-irradiation subgroup and the non-irradiated control group indicating an acceptable radioprotection against the lethal effects of irradiation at the dose of 8 Gy.

The median survival for all treatment subgroups exposed to 9Gy irradiation showed a significant difference with the median survival in the irradiation-only subgroup exposed to 9Gy irradiation (relative radioprotection). However, the median survival difference was significant between all treatment groups exposed to 9Gy irradiation and the non-exposed control group, suggesting inadequate radioprotective effect against lethal effect of 9Gy irradiation (Table 1).

No significant difference was observed between the two doses of 4 and 2 mg/kg administered pre- and post-irradiation in none of 7, 8 and 9 Gy irradiation doses (p>0.05).

The $LD_{50/30}$ and DRF

The $LD_{50/30}$ was obtained to be 7.18 Gy (95% CI: 6.59-7.77) for the irradiation-only group. The $LD_{50/30}$ for all treatment groups and DRFs are shown in Table 2.

Table 2. The LD50/30 and dose reduction factor for all drug groups

Group	$LD_{50/30}$, Gy (95% CI)	Dose reduction factor (DRF)
Irradiation-only	7.18 (6.59 _ 7.77)	
Nanocurcumin 4 mg/kg Pre-irradiation	8.78 (8.14 _ 9.50)	1.22
Nanocurcumin 4 mg/kg Post-irradiation	7.68 (7.01 _ 8.31)	1.06
Nanocurcumin 4 mg/kg Pre- and post-irradiation	7.66 (7.03 _ 8.27)	1.06
Nanocurcumin 2 mg/kg Pre- and post-irradiation	8.11 (7.55 _ 8.68)	1.12

The lack of overlap between the $LD_{50/30}$ 95% CIs of the pre-irradiation nanocurcumin group and the irradiation-only group indicates a significant difference between these two groups, suggesting proper radioprotection. The overlapping of the 95% CI values of other treatment groups with the irradiation-only group reveals that their $LD_{50/30}$ is not significantly different from that of the irradiation-only group, indicating inadequate radioprotection.

DISCUSSION

The ionizing radiation through forming free

radicals imposes severe damage and death of healthy and tumor cells [21, 22]. Since the exposure to radiotherapy or to nuclear radiation accidents induces unwanted side effects, thus the development of radioprotector agents is of great importance [8, 9, 19]. Radioprotectors such as amifostine are compounds whose administration before and even after exposure could reduce the damages and deaths caused by ionizing radiation [9, 19]. Although amifostine has been known as the most effective radioprotector and approved by the FDA for use in head and neck cancer patients, its clinical application is restricted due to serious complications such as nausea, vomiting, hypotension and allergic reactions [23-25]. Additionally, the amifostine cannot be orally administred and should be taken intravenously in the clinical practice [23]. Therefore, developing a non-toxic, inexpensive, and preferably herbal radioprotector with oral administration capability is one of the research priorities of the scientists [19]. Many preclinical laboratory studies have been carried out on various herbal radioprotectors [5-7]. The curcumin due to its unique properties, such as non-toxicity, edibility, and availability possesses special functionality for use in clinic [12, 26, 27].

The concern about the clinical application of curcumin is its low absorption capacity and bioavailability [12, 13]; its recent nanoscale formulation has, however, been able to overcome this problem to a great extent [14-16]. Recently, several clinical studies on SinaCurcumin®, a novel nanomicelle formulation of curcumin, have had promising results for the clinical application of curcumin [28-30]. In an *in vivo* study on mice to find the pharmacokinetic parameters of SinaCurcumin®, the maximum concentration (Cmax) value for nanoformulation and free powder was 2540.62 and 59.07, respectively. In this study, the bioavailability of nanomicelle curcumin was estimated to be 59.2 times higher than its free form (unpublished data).

The gold standard method for assessing the radioprotective effect of a radioprotector and calculating its DRF is to investigate the 30-day survival in the mice exposed to lethal doses of radiation [9, 19, 20]. In a study by Inano and Onoda, the curcumin powder administration pre- and/or post-irradiation was unable to reduce mortality in rats exposed to radiation in spite of inhibiting few acute and chronic effects [31]. In contrast to the study of Inano and Onoda, the use of nanocurcumin formulation in our study was able to reduce the mortality rate in the mice exposed to lethal irradiation doses. Many preclinical studies have been conducted using other endpoints to investigate the effect of newly developed curcumin formulations. Soltani et al. in an *in vitro* study examined the protective effect of nanocurcumin in comparison with its free form on human peripheral blood mononuclear cells (PBMCs) exposed to gamma ray [32]. They showed that the curcumin nanoformulation significantly reduced the DNA damage and lipid peroxidation caused by exposure to irradiation in comparison with the free curcumin group. In an *in vivo* study by Shi et al., the radioprotective effect of liposomal curcumin against pulmonary complications, including pneumonia and pulmonary fibrosis, as well as its sensitizing effect on lung tumor cells were simultaneously shown [33]. They injected the liposomal curcumin (5 mg/kg) to mice systemically for 7 days. The mechanism underlying the radioprotective effects was reported to be inhibition of nuclear factor-κB pathway and reduced expression of inflammatory factors including tumor necrosis factor-α, interleukin (IL)-6 and IL-8.

There is currently no comprehensive agreement on the time when a radioprotector is administered for exposure (i.e. before or after irradiation, or both before and after exposure). Okunieff et al. investigated the protective effect of curcumin against acute and chronic radiation-induced skin damage in the mice administered 5 days pre- and/or post-irradiation [34]. The curcumin taken pre- and post-irradiation showed no increase in the radioprotection of the skin compared to either pre- or post-irradiation groups. In our study, the prolongation of nanocurcumin administration by a week after exposure at the radiation dose of 8 Gy X-ray resulted in a significant reduction in 30-day survival. Further studies are needed to explain the cause of this reduced protective effect. Lethal doses of radiation make the mice particularly weak and sensitive. Perhaps the damage caused by the repeated intragastric gavage up to 7 days post-irradiation in the vulnerable mice can be a possible explanation for this observation.

Improving the efficiency of a radioprotector as a result of its combination with another radioprotector has been shown in various studies [35-39]. Some studies have also reported the

synergistic effect of curcumin in combination with other anticancer drugs such as cisplatin [40-42]. The radioprotective effect of nanocurcumin in combination with other proper phytochemicals such as resveratrol and quercetin remains to be determined.

Various mechanisms have been proposed for the radioprotective effect of curcumin. Curcumin is a potent antioxidant that, in addition to scavenging the free radicals, exerts its protective mechanism through enhancing the expression of antioxidant enzymes [43-45]. In addition, curcumin can result in reduced DNA damage and inhibit transcription of genes involved in the inflammatory responses [46].

CONCLUSION

The oral nanocurcumin administration before irradiation significantly reduced mortality rate in the exposed mice. The distinguished features of nanocurcumin, such as non-toxicity, edibility, and availability make this herbal product a promising radioprotector for use in radiotherapy and radiation accidents. In the light of the recent clinical studies on nanocurcumin [28-30, 47], further extensive trials are needed to confirm the clinical properties of the nanocurcumin.

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