

## Research Article



## Evaluation of Radioprotective Effect of *Garcinia indica* in Mice Exposed to $\gamma$ -Radiation

Ramachandran HD\*

Department of Biochemistry, Bangalore University, Bangalore, Karnataka, India.

\*Corresponding author's E-mail: [drramac5@gmail.com](mailto:drramac5@gmail.com)

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### ABSTRACT

The effect of 0, 5, 7.5, 10, 15, 20, 25, 40, 50 and 80 mg/kg body weight of aqueous extract of *Garcinia indica* administered intraperitoneally was studied on the radiation-induced mortality in mice exposed to 6 Gray of  $\gamma$ -radiation. Treatment of mice with different doses of *G. indica* consequently for five days delayed the onset of mortality and reduced symptoms of radiation sickness when compared with the non-drug treated irradiated controls. The highest protection against gastrointestinal (GI) tract death was observed for 10g of *Garcinia indica*, where the highest number of survivors were reported up to 9 days post radiation, while 10 mg/kg of *Garcinia indica* administered i.p. provided the best protection as evidenced by the highest number of survivors 30 days post-radiation in this group when compared to other doses of *G. indica*. Toxicity study showed that *G. indica* was non-toxic up to doses of 220 mg/kg bw, where no drug-induced mortality was observed. The LD<sub>50</sub> dose i.p. of *G. indica* was found to be 250 mg/kg bw. Our study demonstrated the ability of *G. indica* as a good radio protective agent and the optimum protective dose was 1/25<sup>th</sup> of its LD<sub>50</sub> dose.

**Keywords:** *G. indica*, Gamma radiation, Mice survival, Radioprotection, Toxicity.

### INTRODUCTION

Radiotherapy is the most common modality for treating human cancers. Eighty percent of cancer patients need radiotherapy at some time or other, either for curative or palliative purpose. In the course of treatment, radiation produces numerous biological perturbations in cells namely increased DNA damage in tumor cells, as double strand breaks are important in cell death; altered cellular homeostasis; modified signal transduction pathways and redox state and disposition to apoptosis. These deleterious effects of radiation not only kill the cancer cells but also normal cells. In the process of obtaining better tumor control with a higher dose, the normal tissues have to be protected against radiation injury. Thus, the role of radio protective compounds assumes important in clinical radiotherapy.

With the recognition that normal tissue protection in radio therapy is as important as the destruction of the cancer cells, the focus of protection research becomes more therapy oriented. The use of certain chemical agents may reduce the ill-effects of radiation in such conditions. For the first time ever, it was observed that the pretreatment of rats and mice with cysteine before exposure to radiation protected them against radiation-induced sickness and mortality.<sup>1</sup> Since then, many compounds have been synthesized and tested for their radio-protective ability. In the earlier days only sulphhydryl compounds were found to be superior radio-protectors than the other non-sulphhydryl compounds, but the major drawback of these compounds has been their high toxicity at the optimum protective doses, which precluded their effective use in humans.<sup>2</sup> Although another compound S-3 (aminopropylamino)

ethylphosphorothioic acid exhibited substantial and selective protection of normal tissues with little or no protection to the solid tumors, it was found to be highly toxic at the optimum protective dose and the possibility of using it on a daily basis was not feasible.<sup>3,4</sup> Therefore, it is desirable to search for compounds from natural sources especially plants called phytochemicals that are capable of offering high protection and being less toxic.

Phytochemicals offer an alternative to the synthetic compounds and are considered either non-toxic or less toxic along with producing negligible side effects and this has given impetus to screen for their radio-protective ability. Experience with radio protectors worldwide is that animal studies with death as the end point is the most confirmatory because the 30days time period after lethal whole body irradiation clearly indicates the capacity of the drug in test to modulate the recovery and regeneration of the gastrointestinal epithelium and the haemopoetic progenitor cells in the bone marrow, the two most radiosensitive organs that are essential for sustaining life. The aim of the present study was to evaluate the radio protective effect of various doses of *G. indica* in mice exposed to 6 Gy of whole body  $\gamma$ -radiation considering survival as the end point.

### MATERIALS AND METHODS

The animals were cared and handled according to the guidelines set by the World Health Organization, Geneva, Switzerland and the Indian National Science Association (INSA), New Delhi. Eight week-old male rats weighing 30-35g were selected from an inbred colony maintained under controlled conditions of temperature (28±2°C), humidity (50±5%) and light (12hr, each of light and dark cycle). Throughout the experiment, the animals were



provided sterile water and food *ad libitum*. One polypropylene cage containing sterile paddy husk as bedding housed four animals.

### Preparation of extract

A 70% ethanolic extract of the sun-dried pulp of *Garcinia indica* was used in this study.

### Determination of acute drug toxicity

The acute toxicity of *G. indica* was determined as described below.<sup>5,6</sup> The animals were allowed to fast by withdrawing food and water for 18 hours and the fasted animals were divided into several groups and each group was injected with various doses namely, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300 and 400 mg/kg body weight of freshly prepared extract of *G. indica* intraperitoneally. Animals were provided food and water immediately after administration of the *Garcinia* extract. Mortality of the animals was observed up to 14 days post drug administration. Acute LD<sub>50</sub> of the extract was calculated using a computer programme for probit analysis.

### Effect of *Garcinia* extract on radiation-induced mortality

The animals were divided into two groups. The first group of animals were administered 0.01ml/g bw of sterile double distilled water i.p. the second group of animals were injected i.p with 5, 7.5, 10, 15, 20, 25, 40, 50 and 80 mg/kg bw of *Garcinia* extract consequently for five days.<sup>7</sup>

### Irradiation

One hour after the last administration of double distilled water or *Garcinia* extract on the fifth day, the prostrate and immobilized animals of both the groups were whole body exposed to 0 or 6 Gy of <sup>60</sup>Co radiation (Microtron Centre, Mangalore University) in a specially designed acrylic box. One batch of five animals was irradiated at a time at dose rate of 1.5 Gy/min. The animals were monitored daily up to 30 days post-irradiation for the development of symptoms of radiation sickness and mortality. The statistical significance between the treatments was determined by Students "t" test.

## RESULTS

### Acute toxicity

The administration of different doses of *Garcinia* extract of 200 through 220 mg/kg bw did not induce any mortality during the whole observation period. An increase in the drug dose to 230 and 240 mg/kg bw resulted in a 30% and 20% reduction in the survival of mice, respectively. However, a further increase in the drug dose up to 250 mg/kg bw of *Garcinia* extract resulted in a 50% reduction in the survival of mice. 100% mortality was observed at 260 mg/kg and thereafter up to a dose of 400 mg/kg bw of *Garcinia* extract (Table 1).

### Effect of *Garcinia* extract on the radiation-induced mortality

The mice in different batches were injected intraperitoneally with 0.5, 7.5, 10, 15, 20, 25, 40, 50 and 80 mg/kg bw of *Garcinia* extract, consequently for 5 days either before whole body exposure to 10Gy gamma irradiation or no radiation were monitored daily up to 30 days post-radiation for the development of symptoms of radiation sickness and mortality. The effect of different doses of *Garcinia* extract on the radiation-induced mortality is shown in Table 2, Figure 1 and Figure 2 and the results are expressed as percent survival.

The animal group exposed to only radiation (without administration of *Garcinia* extract), exhibited radiation sickness, one day after exposure to 6 Gy of  $\gamma$ -radiation. The main symptoms included reduction in the food and water intake, irritability, epilation, weight loss, emaciation, lethargy, diarrhea and ruffling of hairs. Facial oedema was also observed in a few animals at the end of first week after exposure. During the second week after exposure some animals exhibited paralysis and difficulty in locomotion. The first mortality in this group was observed on day 2. 90% of the animals died within 9 days of irradiation resulting only in 4% survival by day 30 post-radiation.

The daily administration of 5, 7.5, 10, 15, 20, 25, 40, 50 and 80 mg/kg bw *Garcinia* extract for five consecutive days did not cause any drug-induced mortality. The pretreatment of mice with various doses of *Garcinia* extract either delayed or reduced the severity of radiation sickness. The onset of radiation-induced mortality was also delayed in the irradiated group also given *Garcinia* extract when compared with the irradiated group not given *Garcinia* extract. The shortest delay was observed for 50 and 80 mg/kg bw, where the first mortality occurred on day 4 post-irradiation. The longest delay was observed for 20 mg/kg bw *Garcinia* extract, where the first mortality was observed by day 9 post-radiation (Table 2).

Treatment of mice with various doses of *Garcinia* extract also had an ameliorating effect on the gastrointestinal tract as evidenced by an increase in the 10 day survival of mice, where 5 fold increase was observed for 15 mg/kg, 4 fold for 7.5, 10 and 20mg/kg bw of *Garcinia* extract, 3 for 25 mg/kg and 2.5 fold for 5 and 40 mg/kg *Garcinia* extract (Figure 1). Majority of the animals (80 %) of the irradiated group not administered the extract, died within 10 days after irradiation, while the extract pre-treatment increased the 10 day survival significantly. A lower mortality was observed in the animals treated with 12.5 mg/kg extract before irradiation and this decline in mortality was significant ( $p>0.001$ ). The other doses of extract also reduced the mortality in comparison with the irradiated group not given the extract. However, a significant elevation in the 10-day survival was observed only for 7.5, 10, 12.5 and 20 mg/kg extract ( $p>0.001$ ) treatment. 5 and 25 mg/kg of extract also protected the



mice against radiation-induced mortality. However, the differences were statistically non-significant.

Analysis of thirty day survival revealed a drug-dose dependent increase in the survival of irradiated mice up to a dose of 10mg/kg in the irradiated group given the extract, where a highest survival of 58.33% was observed as compared to the irradiated group not given the extract, where only 4% animals survived at the end of 30

days (Table 2). A further increase in the drug dose to 12.5mg/kg bw resulted in 8.33% reduction in the survival, when compared with the 10mg/kg extract. Increase in extract dose further resulted in a consistent decline in the animal survival reaching an optimum at 50 and 25 mg/kg, where no survivors were reported at the end of 30 days (Figure 1).

**Table 1:** Acute toxicity of the extract of *Garcinia indica* on the survival of mice

G. indica mg/kg	Mortality on different days post drug treatment														Total Animals	Survivors	% Survivors
	1	2	3	4	5	6	7	8	9	10	11	12	13	14			
200	---	---	---	---	---	---	---	---	---	---	---	---	---	---	10	10	100
210	---	---	---	---	---	---	---	---	---	---	---	---	---	---	10	10	100
220	---	---	---	---	---	---	---	---	---	---	---	---	---	---	10	10	100
230	---	---	1	---	---	1	1	---	---	---	---	---	---	---	10	07	70
240	---	---	---	---	---	2	---	---	---	---	---	---	---	---	10	08	80
250	---	2	1	1	1	---	---	---	---	---	---	---	---	---	10	05	50
260	2	2	2	2	1	1	---	---	---	---	---	---	---	---	10	0	0
270	4	3	2	---	1	---	---	---	---	---	---	---	---	---	10	0	0
280	6	3	1	---	---	---	---	---	---	---	---	---	---	---	10	0	0
300	7	2	1	---	---	---	---	---	---	---	---	---	---	---	10	0	0
400	10	---	---	---	---	---	---	---	---	---	---	---	---	---	10	0	0

**Table 2:** Effect of various doses of *Garcinia indica* on the survival of mice exposed to 6 Gray of  $\gamma$ -radiation.

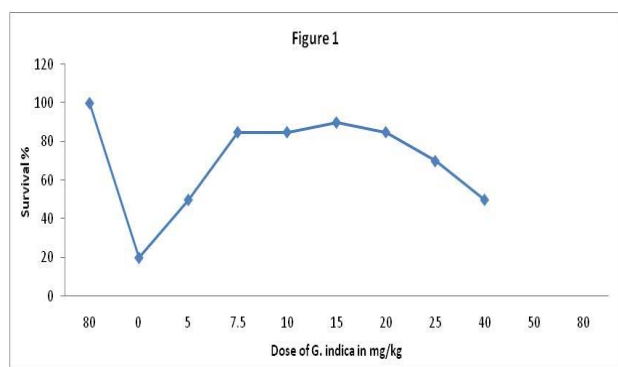
G. indica mg/kg	Mortality on different days post-irradiation days															Number of Survivors	Total no. of animals
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
0	-	3	3	3	2	2	2	2	1	-	-	1	-	-	-	1	20
5	-	-	-	-	2	-	2	-	-	-	-	1	-	1	-	4 <sup>a</sup>	10
7.5	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	5 <sup>b</sup>	10
10	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	7 <sup>c</sup>	10
15	-	-	-	-	-	-	-	1	-	-	1	-	1	-	-	6 <sup>c</sup>	10
20	-	-	-	-	-	-	-	-	1	-	1	-	-	-	1	4 <sup>a</sup>	10
25	-	-	-	-	-	-	-	2	2	-	-	-	1	-	-	4 <sup>a</sup>	10
40	-	-	-	-	-	2	2	-	-	-	-	1	-	1	-	3	10
50	-	-	-	3	-	3	2	-	1	1	-	-	-	-	-	0	10
80	-	-	-	4	4	1	-	-	-	1	-	-	-	-	-	0	10

P < a = 0.02; b = 0.01 and c = 0.001

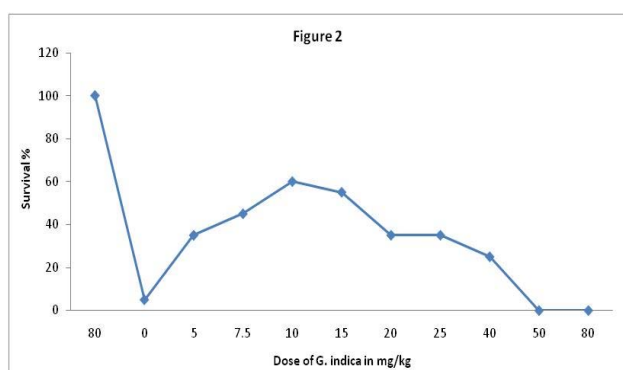
**Table 2:** Effect of various doses of *Garcinia indica* on the survival of mice exposed to 6 Gray of  $\gamma$ -radiation (Continued...)

G. indica mg/kg	Mortality on different days post-irradiation days															Number of Survivors	Total no. of animals
	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30		
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	20
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4 <sup>a</sup>	10
7.5	-	-	-	-	1	-	1	-	1	-	-	-	-	-	-	5 <sup>b</sup>	10
10	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	7 <sup>c</sup>	10
15	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6 <sup>c</sup>	10
20	-	1	-	2	-	-	-	-	-	-	-	-	-	-	-	4 <sup>a</sup>	10
25	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	4 <sup>a</sup>	10
40	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	10
50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	10
80	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	10

P < a = 0.02; b = 0.01 and c = 0.001



**Figure 1:** Effect of various doses of *G. indica* extract on the radiation-induced mortality in mice exposed to 10Gy radiation (10 days survival)



**Figure 2:** Effect of various doses of *G. indica* extract on the radiation-induced mortality in mice exposed to 10Gy radiation (30 day survival).

Garcinia extract administration before irradiation increased the survival significantly for 5 to 25 mg/kg ( $p < 0.02$  to  $0.001$ ). However, the number of survivors was highest (58.33%) after pretreatment of mice with 10mg/kg of Garcinia extract, and hence it was considered the optimum dose for radioprotection. The optimum radio protective dose of 10 mg/kg of Garcinia extract was found to be 1/250 of the LD<sub>50</sub> dose (250 mg/kg bw), which was far below the LD<sub>50</sub> dose.

## DISCUSSION

Ayurveda, the Indian system of medicine concept appeared and developed between 2500 and 500 BC in India. The literal meaning of Ayurveda is "science of life," because ancient Indian system of health care focused views of man and his illness. It has been an integral part of Indian culture and material medica and extensively uses plant-derived compounds / phytochemical extracts; individually and in combination for the treatment of various disorders and diseases.<sup>8</sup> These extracts/ phytochemicals are such that they possess the desired activity with the adequate potency and are devoid of untoward side effects. The animals of the irradiated group exhibited signs of radiation sickness including reduction in food and water intake, irritability, epilation, weight loss, lethargy and diarrhea. The death of 90% of animals exposed to 10Gy radiation within 9 days is due to functional failure of the gastrointestinal tract. The

remaining animals died within the next 20 days exhibiting haemopoetic syndrome and the characteristic symptoms like epilation, weight loss, and lethargy and ruffling of hairs.<sup>9,10</sup> It is a well established fact that ionizing radiation can induce at the cellular level in the biological important macromolecules such as DNA, proteins, lipids and carbohydrates in various organs. While some damage is expressed early others expressed over a period of time depending on the cell kinetics and radiation tolerance of the tissue. Similar to chemotherapy, the effect of whole body irradiation is mainly felt by the highly proliferating germinal epithelium, gastrointestinal epithelium and the bone marrow progenitor cells. Of these, the germinal epithelium does not have a life supporting function to the exposed individual, while the gastrointestinal epithelium and the bone marrow progenitor cells are crucial for sustenance of life and any damage to these cells will impair the normal physiological processes drastically. The GI epithelium is less sensitive than the bone marrow progenitor cells but as the cell transit time is quick, it is expressed earlier than the haemopoetic syndrome.<sup>9</sup> In mice, death within 10 days post-radiation is due to gastrointestinal damage.<sup>10,11</sup> The bone marrow stem cells are more sensitive to radiation damage the intestinal crypt, but the peripheral blood cells have a longer transit time than the intestinal cells and hence the gastrointestinal syndrome appears earlier than the bone marrow syndrome and in mice due to irradiation from 11 to 30 days is due to the haemopoetic damage influenced by radiation.<sup>9,10</sup>

The pretreatment of mice with different doses of Garcinia extract resulted in a dose dependent reduction of radiation-induced mortality up to 10mg/kg bw and a further increase in the drug dose resulted in the decline in the animal survival when compared with the 10mg/kg bw of extract. Earlier studies on radioprotection have shown that an agent in test acts only at a particular dose range and above which it may not be protective and sometimes can even prove to be toxic.<sup>12</sup> The active principle of *Plumbago rosea*, the plumbagin at pico and femto gram range has been reported to stimulate granulocytes *in vitro*, while at higher doses it had immunosuppressant activity.<sup>13</sup> The reason for this may be that after a particular concentration, a compound instead of being an antioxidant may act like pro-oxidant, inducing toxic symptoms, resulting in death. This is the reason that Garcinia extract has optimum protection at mg/kg bw and the higher doses result in the decline in the protective action of the same. The Garcinia extract pretreatment provided protection against radiation sickness and mitigated the sufferings of the animals. Research regarding the use of Garcinia extract to protect against radiation damage is not available. Tripathi *et al*, have reported pretreatment with *Syzygium cumini* (Blue plum/ Jamun) extract significantly inhibited the frequencies of aberrant metaphases, CAs, MN formation, and cytotoxicity in mouse bone marrow cells induced by cyclophosphamide (CP).<sup>14</sup> It also produced a significant



reduction of abnormal sperm and antagonized the reduction of CP-induced SOD, CAT, and GSH activities and inhibited increased MDA content in the liver. They have observed that the extract has a protective effect against genotoxicity and oxidative stress induced by CP. The leaf extract of *Syzygium* has been demonstrated to protect against radiation-induced DNA damage as evidenced by a significant decline in the micronuclei-induction in radiation-exposed human lymphocytes when compared with the non-drug treated irradiated lymphocyte cultures by Jagetia and Baliga.<sup>15</sup>

The pattern of survival in irradiated group fed *Garcinia* extract was similar to that of the irradiated control group except that mortality was delayed. This clearly indicates the effectiveness of *Garcinia* extract in arresting GI death, where the number of survivors for 5, 7.5, 10, 15, 20, 25, 40 and 50 mg/kg bw was higher than that of the irradiated control. The reduction in GI death may be due to the protection of intestinal epithelium, which would have allowed proper absorption of the nutrients. Our findings support the contention that *Garcinia* may protect the GI tract epithelium against the toxic insult of radiation, thus protecting against GI death in this study. Lei et al., 2012 have reported the attenuation of radiation-induced intestinal damage by mangeliferin aglycone.<sup>16</sup>

The pretreatment of mice with *Garcinia* extract significantly reduced the bone marrow deaths in the irradiated, *Garcinia* fed group, especially at a dose of 5 to 25 mg/kg, where a significant elevation in the survival has been observed. This increase in the 30 day survival has been observed. This increase in the 30 day survival may be owing to the protection afforded by the *Garcinia* extract to the bone marrow stem cell compartment, which continued to supply the requisite number of cells in the survivors. The bone marrow cells have been reported to be protected against the radiation-induced damage by various other plant formulations.<sup>17-20</sup> *Garcinia*, like another plant *Phyllanthus emblica* has also been found to be immunomodulatory (unpublished results) and this would have increased the body's defense system by increasing the immunity.<sup>20,21</sup> Further the antimicrobial action of *Garcinia* would have prevented the localization of pathogenic microbes in the GI tract and bacterial infection, resulting in the observed radioprotection.<sup>21</sup> *Phyllanthus* has also been found to be rich in ascorbic acid content and ascorbic acid has already been reported to reduce radiation-induced sickness and mortality and to protect bone marrow cells against the radiation-induced chromosome damage.<sup>22-24</sup> It also contains ellagic acid, which has been reported to decrease bone marrow micro nuclei formation in mice and flavonoids, a class of compounds reported to possess antioxidant and free radical scavenging activities.<sup>25-27</sup> Certain flavonoids have been found to protect against radiation-induced DNA damage.<sup>17, 28-30</sup>

The exact mechanism of action of *Garcinia* extract is not known. However, it may scavenge free radicals produced by radiation and thus reduce radiation-induced damage to the cellular DNA. The presence of hydroxy citric acid flavonoids may be responsible for this action as these compounds are reported to protect DNA from radiation-induced micronuclei in mice.<sup>18</sup> Several phytochemicals have exhibited Nitric Oxide (NO) scavenging activity. *Phyllanthus* has been reported to be a potent inhibitor of lipid peroxidation and scavenger of hydroxyl and superoxide radicals.<sup>31, 32, 33, 34</sup> The presence of various antioxidant compounds in *Garcinia* might have been responsible for the observed radioprotection by scavenging of free radicals generated by radiation exposure.<sup>35</sup> Alternatively, *Garcinia* might have increased the intracellular level of GSH and stimulated the immune systems which could have provided protection against the radiation-induced mortality, being validated in our laboratory (unpublished results).

## CONCLUSION

From the present study it is clear that *Garcinia* extract, a plant based formulation provided protection against the radiation-induced sickness and mortality and the optimum protective dose of 15 mg/ kg bw i.p. is far below the LD<sub>50</sub> (250 mg/kg bw) dose. The exact mechanism of action of the *Garcinia* extract is not known. However, it may scavenge the free radicals produced by radiation and thus inhibit radiation-induced damage to the cellular DNA. Scavenging of NO radicals *in vitro* by *Garcinia* extract is in the process of being tested in our laboratory and this will validate that one of the mechanisms of radioprotection by *Garcinia* may be owing to the scavenging of free radicals generated by radiation exposure. Alternatively, it may also increase GSH levels and may reduce the radiation-induced lipid peroxidation (unpublished results). Since significant protection is obtained at very low non-toxic dose, the extract may have an advantage over the known radio-protectors available so far. Studies are planned to explore the applicability of *Garcinia* in cancer treatment by looking for the preferential protection to the normal tissues and its clinical applicability for cancer cure in the fractionation regime. Since this extract has been used regularly in households of some parts (west coastline) of the country (India), its clinical acceptability should not pose a problem.

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**Corresponding Author's Biography: Dr. H D Ramachandran**



Dr. H D Ramachandran, *M.Sc., Ph.D., FSPR.*, Associate Professor in the Department of Biochemistry, Bangalore University has completed his Master's and Doctoral degrees in Biochemistry from University of Mysore and Central Food Technological Research Institute (CFTRI), Mysore, respectively. He has received grants from various agencies like UGC, DST, DAE- BRNS, DBT for various projects. The areas of research undertaken in his laboratory include lipid biochemistry, oxidative stress and phytochemicals as antioxidants, nanobiotechnology.