

## Reply to P. Bhandari

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All the authors thank Dr. Bhandari for comments on our recently published review, “*Normal tissue protection for improving radiotherapy: where are the gaps?*” We agree that opportunities for discovery and development of radioprotectors and mitigators include plant sources, which is an underexplored area. Our paper wasn’t intended to be an exhaustive review of radioprotectors/mitigators, but rather to present examples of important adverse effects of radiation therapy and current approaches and limitations of using radioprotectors/mitigators to improve treatment outcome and quality of life. Exploration of plant sources for radioprotective properties presents both scientific and economic opportunities and challenges, as noted by Dr. Bhandari.

First, as highlighted in our review, it is important that the agent protect only normal tissues, and not tumors. We agree that innovative strategies are warranted to identify potent and safe radioprotectors. However, the presumption that all natural compounds are safe is not accurate. For example, the potent toxin ricin is a plant product. Every agent, natural or synthetic, should be considered toxic unless proven otherwise at the doses required for protection.

Second, concentration of a given protective ingredient(s) in any natural compound may vary with strain of the plant from which it is extracted, source, age, location, season of harvest, method of extraction, etc. This is particularly a problem with crude extracts, and highlights the importance of quality control and the need to isolate the active component, as discussed in a recently accepted paper that reported the results of preclinical studies on a Chinese herbal medicine formulation, PHY906 (1).

Third, the work on indigo wood root extract is still preliminary, as Dr. Bhandari points out. Before repeating the clinical study using this plant source, additional studies in mice are needed to determine if there is improved survival and absence of tumor protection. On a minor note, since the abbreviation IR is often used for ionizing radiation, its use for indigo root extract may be confusing.

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### References

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