Botanical Medicines and Ionizing Radiation

Part 2—Radiosensitizing Herbs

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Abstract

Isolated herbal constituents have been studied preclinically to enhance the efficacy of radiation therapy in numerous models. However, the few studies on combinations of constituents or extracts that are closer to whole plants have generally shown better results than those seen in studies of these isolated constituents.

Isoflavones from *Glycine max* (soy), also found in other legumes, are a case in point, with isolated genistein actually aggravating cancer metastasis, while mixed isoflavones have been radiosensitizing and have inhibited metastasis. In humans, soy isoflavones have offset the negative effects of radiation therapy without having been truly assessed for radiosensitization, but there is, at least, no indication of interference with radiation at this early juncture. There is some evidence that radiosensitizing herbs may be radioprotective for healthy cells. Curcumin from *Curcuma longa* (turmeric) is in clinical trials that combine this herb with radiotherapy.

Other compounds and herbs of interest as radiosensitizers reviewed in this article are withaferin A and *Withania somnifera* (ashwagandha); berberine and herbs that contain this substance (which has also been primarily radioprotective in human studies without affecting radiotherapy efficacy); artemisinin and *Artemisia annua* (sweet Annie, *qing hao*); *honokiol* and *Magnolia officinalis* (*houpu*); sulforaphane from cruciferous vegetables; and herbal vasodilators. Much work remains to be done to determine if any of these compounds or herbs have roles in clinical radiosensitization.

Introduction

Part 1 of this article[1] reviewed some herbs that may protect the body against the harmful effects of ionizing radiation. Part 2 discusses herbs that can augment the desired effects of ionizing radiation, when used intentionally and principally as cancer therapy. Although radiotherapy has drawbacks and is not necessarily effective in all cases, all kinds of practitioners can agree that, if it is used, its effects should be optimized. Part 2 looks both at herbs that specifically enhance the benefits of radiotherapy and—in some cases—protect healthy cells against the detrimental impacts of radiotherapy. Unfortunately, there are almost no clinical trials on herbal compounds used for radiosensitization, so much of this information remains in the realm of empirical speculation and extrapolation from preclinical studies.

Ionizing radiation resistance is mediated by many mechanisms. Hypoxic conditions around tumor cells, particularly those with increased distance from blood vessels, makes these cells relatively resistant to radiotherapy.[2,3] Cancer cells retain some ability to repair DNA strand breaks induced (directly or indirectly) by ionizing radiation. Neoplastic cells in the relatively radiation-resistant S phase of the cell cycle can survive and subsequently enter back into other phases of the cycle (cell redistribution).[4] Cancer stem cells, which are relatively quiescent cells inside of solid tumors that can repopulate such tumors even if more metabolic cells are killed, may also play a role in radioresistance.[5] Figure 1 summarizes how ionizing radiation induces apoptosis in cancer cells and how herbal medicines can modify this process.

Glycine max (Soy) and Isoflavones

All legumes contain isoflavones, which are famous for being phytoestrogens but have also shown anticancer and cardiovascular protective actions in numerous studies. There is also evidence that legumes enhance the efficacy of radiotherapy. Research in rodents found that combinations of isoflavones, alone and in combination with radiotherapy, increase apoptosis in prostate-cancer cells.[6]

However, genistein alone actually increased metastasis in this model. Daidzein specifically seemed to be important in combination for preventing problems caused by genistein used in isolation.[7] This, at least, supports using combinations of isoflavones, if not whole-plant medicines. As noted below, many isolated plant compounds are being studied, but researchers rarely consider what happens if a whole-plant medicine or

more complex extracts are used, giving the false impression that only isolated constituents are effective or that they are inherently superior.

One clinical trial investigated the effect of soy isoflavones on men with prostate cancer, who were undergoing external-beam radiation.[8] Forty men were randomized to receive 100 mg of soy isoflavones b.i.d or placebo for 6 months during the course of many radiation treatments; however, data from only 26 men were available for full assessment. Compared with baseline, men who received the soy isoflavones had a median prostate-specific antigen (PSA) decline of 76% after radiotherapy versus the 59% median decline that occurred in the placebo group. This shows some promise for enhancing the effects of radiation although the sample size in this study was too small to detect a significant difference. Adverse effects of radiotherapy—including urinary incontinence, erectile dysfunction, cramping/diarrhea, and pain with bowel movements—were all lessened in the isoflavone group, compared with what occurred in the placebo group. This provides preliminary evidence of a generally beneficial effect of soy isoflavones taken during radiotherapy.

One of the ways that isoflavones appear to enhance radiotherapy is by inhibiting the cancer cell's mechanisms for DNA repair. In a non–small-cell lung-cancer model, a number of these mechanisms were blocked by isoflavones, leading to greater apoptosis when these cells were subjected to ionizing radiation.[9]

Curcuma longa (Turmeric) and Curcumin

Turmeric is a member of the Zingiberaceae family and was originally found on the Indian subcontinent and across Southeast Asia. This plant's rhizome contains curcumin, a spicy, resinous mixture that has been studied extensively and has shown

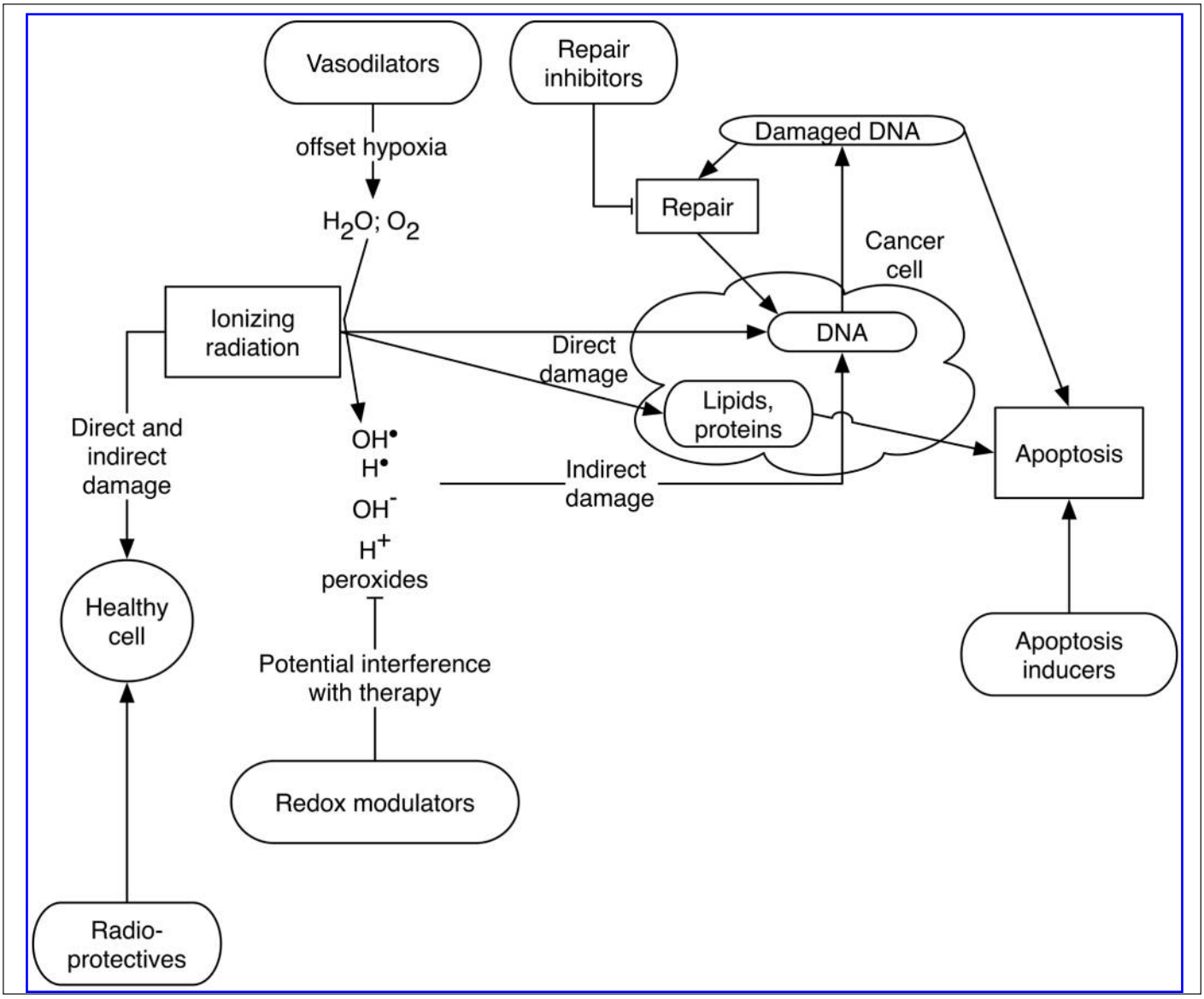

Figure 1. Radiation damage, radiosensitization, and radioprotection. Note: Arrows with flat ends signify inhibition.

both radiosensitizing and radioprotective properties.[10] It is unfortunate that researchers have not looked at the whole rhizome or more-complex extracts from the plant to determine whether the whole rhizome or these extracts might be superior to simple curcumin.

In a nude mouse model of colon cancer, combining curcumin with radiotherapy resulted in significantly better results.[11] Suppression of NFκB was critical for achieving this beneficial outcome. Similar results and mechanisms were seen in a mouse model of prostate cancer.[12] In vitro curcumin radiosensitized human cervical, neuroblastoma, and squamous-cell cancer cells.[13–15]

In various healthy human tissues, including lymphocytes, curcumin prevents radiation-induced damage.[16] In healthy mice exposed to whole-body radiation, curcumin prevented bone-marrow damage and other toxic effects while speeding wound healing.[17–19] In rats exposed to abdominal radiation, curcumin prevented ileal mucosal damage.[20] In rodents whose tongues were radiated, curcumin protected the animals against oral mucositis.[21]

Given this overwhelming amount of preclinical information, it is astonishing that no human studies appear to have been conducted with curcumin and radiation. Clinical trials are underway, or were recently completed but not yet published, to determine if curcumin could offset radiation dermatitis in two settings (trials NCT01042938 and NCT01246973 at clinical trials.gov) and in combination with radiochemotherapy and surgery for rectal cancer (NCT00745134). A typical dose of turmeric powder is 5 g, b.i.d.–t.i.d. during radiation therapy. Curcumin is typically dosed at 1–3 g, b.i.d.–t.i.d.; and, now, phytosomal curcumin (that is, mixed with phosphatidylcholine) is available and is given in doses of 1 g t.i.d. because of the mixture's improved absorption.[22] Curcumin is also frequently combined with black or long pepper or bromelain to enhance its absorption.

Curcuma longa (turmeric).

Glycine max (soy).

Withania somnifera (Ashwagandha)

Ashwagandha is a shrub in the Solanaceae family and is native to the Indian subcontinent. This plant's roots are used as an esteemed medicine, known in the West as an adaptogen and in Ayurvedic medicine as a *rasayana* (an herb used specifically to vitalize and strengthen the body). Although such herbs are radioprotective in healthy cells (as reviewed in Part 1 of this article[1]), these herbs enhance the toxicity of ionizing radiation in cancer cells. In a human lymphoma-cell line, the ashwagandha-derived triterpenoid saponin withaferin A (see Fig. 2) was effective for enhancing apoptosis in these cells, when used in combination with X-rays.[23] Healthy human macrophages were not harmed by this combination in the same study. In this model, withaferin A interfered with cell redistribution in response to X-rays, mediated, in part, by effects on cyclins A, B, and E. Withaferin A combined with radiation also increased levels of oxygen-free radicals in the lymphoma cells. Very similar findings were reported in a renal-cell carcinoma cell line.[24]

In a mouse model of malignant melanoma, intraperitoneal (i.p.) injection of withaferin A (30 mg/kg) 1 hour prior to radiotherapy showed greater activity than withaferin A alone, although no complete tumor eradication was seen.[25] Adding local hyperthermia to this combination, in another mouse study, led to complete tumor eradication in 37% of the animals, and 64% of their fibrosarcomas were completely eliminated.[26] A combination of radiotherapy, hyperthermia, and withaferin A (15 mg/kg) produced the best survival in another study of melanoma in mice.[27] An ethanol extract of whole ashwagandha root (500 mg/kg) injected i.p. into mice with sarcoma had much better effectiveness when combined with hyperthermia and radiotherapy than any treatment alone.[28]

One cautionary note is important: withaferin A increased bone-marrow toxicity of whole-body irradiation of healthy mice in one study.[29] It might be safer to use whole ashwagandha extracts than risk toxicity of isolated constituents.

No clinical trials have been conducted on the use of ashwagandha or any compound from it as a radiosensitizer in humans. Dr. Yarnell has given a tincture of fresh root of ash-

Artemisia annua (sweet Annie).

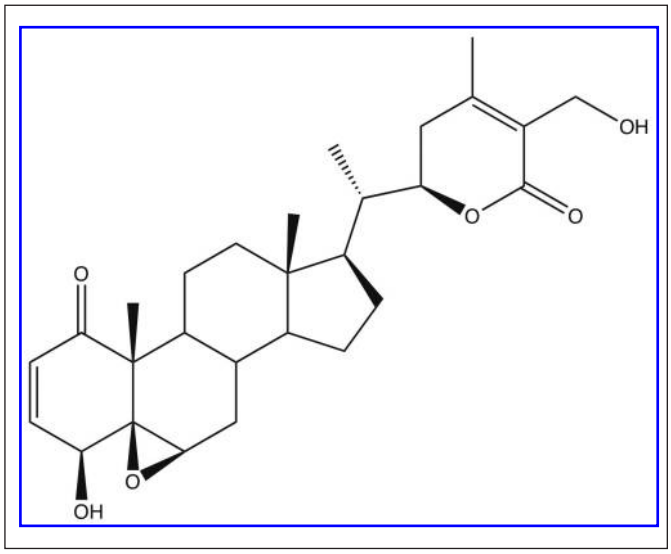

Figure 2. Withaferin A, a triterpenoid saponin from *Withania somnifera* (ashwagandha).

wagandha (0.5–1 tsp t.i.d.), or capsules of dried root (1–2 g b.i.d.) if tincture was not tolerated, to several patients with prostate cancer who were undergoing radiotherapy over the years. There was no difficulty involved with this treatment, and it did seem to be helpful, although many other adjunct treatments were given in these cases. At least two human trials have shown that ashwagandha crude extracts have immunomodulating effects that would also be relevant for treating patients who have cancer, so it seems even more reasonable to consider these extracts as part of protocols for patients who are undergoing cancer radiotherapy.[30,31]

Berberine

Berberine is an isoquinoline alkaloid found, famously, in *Hydrastis canadensis* (goldenseal) and *Berberis aquifolium* (Oregon grape) among other herbs. Berberine has potentiated sensitivity of glioblastoma multiforme cells to X-rays without doing so in healthy human glial cells in vitro.[32] Berberine radiosensitized esophageal cancer cells in vitro by inhibiting a DNA-repair protein known as Rad51, a component not found in healthy cells' DNA repair systems.[33] Berberine radiosensitized hepatoma cells in vitro, although this effect was blocked by the antioxidant *N*-acetylcysteine.[34] Once again, mixtures of alkaloids from plants containing berberine or whole-plant extracts do not appear to have been looked at, so we are left to guess what might be clinically superior.

Most human research on berberine with radiotherapy has focused on this substance's radioprotective actions. A group of 78 patients—with seminomas, abdominal lymphomas, or cervical cancer treated with radiation that affected the intestines—were randomly assigned to be given berberine (300 mg t.i.d.) or placebo for 2 weeks during radiotherapy.[35] Fatigue, proctitis, colitis, diarrhea, and vomiting were significantly less frequent and less severe in the berberine group, compared with what occurred in the control group. There were no obvious adverse effects of berberine. No data on survival rates were given for that study.

In a similar trial of 85 patients with non–small-cell lung cancer, patients were randomly assigned to be given either berberine (20 mg/kg q.d.) or placebo for 6 weeks during radiotherapy.[36] Some patients, but not all, also received chemotherapy. At 6 weeks and 6 months, radiation-induced lung injury of any grade was significantly less common in the berberine group, compared with what occurred in the placebo group. There was no difference in survival rates between the two groups, which does not support the concept of a radiosensitizing effect, but, at least, there was no interference. This is contrary to animal studies that previously showed that berberine was radiosensitizing and protective after abdominal radiotherapy and had these effects in studies on lung cancer treated with radiation.[37,38]

Miscellaneous

Many other herbal agents have been reported in preclinical research to be radiosensitizing. These are discussed below.

Artemisia annua (sweet Annie) contains the compound artemisinin—famous for its antimalarial effects—which is now being studied as an antineoplastic. The semisynthetic version of this compound (artesunate) has been shown to be radiosensitizing in vitro and in rodents against non–small-cell lung cancer.[39]

Honokiol is a well-researched lignan found in *Magnolia* spp. (*houpu*) flowers, leaves, and bark. This lignan had previously shown antineoplastic activity. In a mouse model of lung cancer, liposomal honokiol (with added lecithin, cholesterol, and polyethylene glycol) was synergistic with radiation in delaying tumor growth and prolonging survival in one study.[40] Honokiol was shown to inhibit hypoxia-inducible factor 1α and was synergistic with radiation in a mouse model of colon cancer as well.[41]

The seeds of the *Azadirachta indica* (neem) tree from India and its neighbors yields an expressed oil that has been shown to be a radiosensitizer in an in vitro model.[42] This model did use anaerobic conditions, which do not mirror the real environments of most tumors. A neem leaf extract was radiosensitizing for neuroblastoma cells in vitro, partially through increasing proapoptosis pathways and partly through inhibiting survival signals.[43]

Sulforaphane, an isothiocyanate found in cruciferous vegetables, has been shown to sensitize human cervical-cancer cells to radiation in vitro.[44] This action appears to result, in part, from inhibition of repair to damaged DNA by the cancer cells. Sulforaphane given to mice with implanted cervical-cancer cells also acted as a radiosensitizer in this study. Another study found sulforaphane to be radiosensitizing in head-and-neck cancer cells in vitro.[45]

Because tumors tend to be hypoxic with low blood flow, it is possible that vasodilating herbs will increase flow into the area bringing more blood and thus more oxygen.[3] Increased oxygenation should augment radiation therapy. Thus, vasodilating herbs, such as *Crataegus* spp. (hawthorn), *Tilia* spp. (linden), *Achillea millefolium* (yarrow), *Encelia farinosa* (incienso), *Ammi visnaga* (khella), *Rosmarinus officinalis* (rosemary), and *Ginkgo biloba* should all be investigated as radiosensitizers.

Conclusion

For the most part, the potential of using herbs or herbal compounds as radiosensitizers remains theoretical. Most research has focused very narrowly on single isolated constituents, although there are cautionary tales from existing work that this might be harmful or not as effective as more-complex extracts would be. It is likely that concerns about interference with radiotherapy by natural products has limited research in this area. This is largely based on trials of synthetic isolated antioxidants suggesting interference with efficacy of radiotherapy.[46] However, plant compounds are not simply antioxidants and should be tested on their own merits, given preclinical and some clinical research suggesting that these compounds are safe to combine with radiotherapy. The substances and herbs mentioned in this review would be good places to start with more substantial clinical trials. ■

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