Radioprotective potential of mint: A brief review

ABSTRACT

Radiation is an important modality in cancer treatment and estimates are that between one third and one half of all patients will require ionizing irradiation therapy during some point in their clinical management. However, the radiation-induced damage to the normal tissues restricts the therapeutic doses of radiation that can be delivered to tumors and thereby limits the effectiveness of the treatment. The use of chemical compounds (radioprotectors) represents an obvious strategy to improve the therapeutic index in radiotherapy. However, most of the synthetic radioprotective compounds studied have shown inadequate clinical application owing to their inherent toxicity and high cost. These observations necessitated a search for alternative agents that are less toxic and highly effective.

Studies in the recent past have shown that some medicinal plants possess radioprotective effects. Two species of the commonly used aromatic herb mint, Mentha piperita and M. arvensis protected mice against the γ-radiation-induced sickness and mortality. Detailed investigations have also shown that the aqueous extract of M. piperita protected the vital radiosensitive organs: the testis, gastrointestinal and hemopoetic systems in mice. The radioprotective effects are possibly due to free radical scavenging, antioxidant, metal chelating, anti-inflammatory, antimutagenic, and enhancement of the DNA repair processes. This review for the first time summarizes the observations and elucidates the possible mechanisms responsible for the beneficial effects. The lacunae in the existing knowledge and directions for future research are also addressed.

KEY WORDS: Mentha piperita, Mentha arvensis and Mint oil, plants, radioprotection

INTRODUCTION

Radiotherapy is an important treatment modality for cancer and depends on the stage of the tumor, its localization and general health of the patient; it may be used as a single modality or as an adjuvant along with surgery and/or chemotherapy. However, effective use of ionizing radiation is compromised by the side effects that result from radiation-induced damage to normal tissue. This includes the acute destruction of rapidly proliferating cells in radiosensitive tissues (lymphoid organs, bone marrow, intestinal crypts, testes, and ovaries) and long-term fibrotic damage to the soft tissues that progressively limit their function.

The use of radioprotective compounds, which can selectively protect normal tissues against radiation injury, is of immense use as, in association with protecting the normal tissue, it will also permit use of higher doses of radiation to obtain better cancer control and possible cure. However, till date no ideal radioprotectors are available as most synthetic compounds, including the Food and Drug Administration (FDA), USA, approved aminothiol, S-2-(3-aminopropyl-amino) ethyl phosphorotheioic acid, [WR-2721, amifostine, ethiophos (USA), or gammaphos (former USSR)], are toxic at their optimal concentrations. Obviously, there has been limited success of these agents in clinics.

The herbal drugs offer an alternative to the synthetic compounds and are considered either non-toxic or less toxic than their synthetic counterparts. Plants and their phytochemicals, especially with free radical scavenging, antioxidant properties, and immunostimulatory effects have been evaluated for their radioprotective effects. Preclinical studies in the past two decades have shown that some commonly used medicinal plants and their phytochemicals possess radioprotective effects.

MINT AS A RADIOPROTECTIVE AGENT

Mint (peppermint) [Figure 1], a perennial aromatic herb belonging to the family Labiatae and genus Mentha is an important culinary plant with immense medicinal use. The plant which was originally a native to Europe was carried to different parts of the world through travelers, warriors, and traders. Today, Mint is cultivated in North America, Africa, Australia, and Asia mainly for its pharmaceutical, medicinal, and culinary uses. Globally, the essential oil obtained by steam
**Phytochemicals in Mint**

Irrespective of the plant species, the phytochemicals present in the various species of Mentha are the same while their ratios may alter. Mint plants contain over 40 distinct chemical compounds and are addressed herewith.

The essential oil of peppermint is mostly made up of menthol, menthone, menthyl esters, 3-carene, carvone, cis-carane, cis-pinane, isomenthone, limonene, menthol, myrcene, and the monoterpene derivatives pulegone, pipertone, menthofuran, trans-cinnamic acid, oleomorphic acid, p-cymene, phycion, terpinolene, and ursolic acid. (Figure 2)

Mint also contains α-pinene, β-pinene, cineole, jasmon, ledol, limonene, neomenthol, pipertone, pulegione, and viridiflorol. Menthol and menthyl acetate are responsible for the pungent and refreshing odor while the ketones menthone, pulegone, menthofuran have a less delightful fragrance. Traces of jasmon improve the oil’s quality and radioprotective potential. (Figure 2)

The mint plants also contain the flavonoids acacetin, chrysoeriol, diosmin, eriocitrin (eriodictoyl-7-o-rutinoside), hesperidin, hesperidoside, isorhoifolin, linarin, luteolin, menthoxide, methyl rosmarinate, rutin, tiliani, narirutin, and nodiflorene. The phenolic acids present are cafeic acid, lithospermic acid, rosmarinic acid, protocatechuc acid, protocatechuc aldehyde, phytosterols, β-sitosterol, and daucosterol; the anthraquinones aloe-emodin, chrysophanol, emodin, and tannins are the other compounds present. (Figure 2)

**Scientifically Validated Studies**

Scientific studies have shown that mint and its oil reduces smooth muscle contractions through a calcium channel blocking effect. This then causes the antispasmodic effect on the smooth muscles of the gastrointestinal tract. Mint also relaxes the smooth muscles of the gastrointestinal tract by reducing the cellular calcium influx. Menthol, the active principle is reported to be antibacterial, stimulates bile flow, reduces the tone in the esophageal sphincter, facilitates belching, and acts as a carminative. Mint also possesses neuromodulatory and performance-enhancing properties. Mint oil modulates the calcium channel-dependent processes in intestinal, neuronal, and cardiac preparations. It decreases travel sickness, stimulates bile flow, and assists digestion.

Experimental studies have shown that mint also possess cancer preventive properties against the shamma-induced oral carcinogenesis in the hamster cheek pouch model and benzo[a]pyrene-induced lung tumors in mice. Clinical studies have shown that mint is effective in ameliorating the various gastrointestinal disorders to avoid or mitigate the irritable bowel syndrome and in preventing digestive disorders like dysentery, flatulence, and gastritis.

**Radioprotective Potential of M. Arvensis and M. Piperita and Survival Studies**

Among all available experimental assays, animal survival as the end point is the most confirmatory in radioprotective studies. This is because this assay clearly indicates both quantitative and qualitative degree of the radioprotective...
effects of a test compound. Jagetia and Baliga\cite{18} for the first time observed that the chloroform extract of *M. arvensis* protected mice against the radiation-induced sickness and mortality.\cite{18} The optimal effect was seen at 10 mg/kg of mint extract and the dose reduction factor (DRF) was observed to be 1.2 when administered intraperitoneally for five consecutive days before exposure to different doses of $\gamma$-radiation (6 to 12 Gy). The drug was non-toxic up to a dose of 1,000 mg/kg body weight, thereby confirming that the optimal dose was safe and did not possess drug-induced toxicity.\cite{18}

Studies have also shown that the oil as well as the aqueous extract of *M. piperita* possesses significant radioprotective properties.\cite{19,20} Oral administration of the oil and the aqueous extract of the plant for three consecutive days protected mice against the radiation-induced sickness and mortality.\cite{19,20} The aqueous extract, at 1g/kg b. wt. was observed to have offered a comparatively high DRF of 1.78.\cite{19}

In rodents, death within 10 days post-irradiation is due to the gastrointestinal epithelial damage, while that from 11 to 30 days post-irradiation is because of hemopoietic damage.\cite{18} From these studies, it is evident that both *M. arvensis* and *M. piperita* protected mice against both gastrointestinal and bone marrow deaths. Mint also prevented radiation-induced weight loss and emaciation in these studies suggesting that, irrespective of the polarity (chloroform and aqueous extracts), the radioprotective effects were significant. Following these observations a series of preclinical studies by Ashok Kumar, Ravindra Samarth and colleagues have shown that mint protects the vital organs against the radiation-induced ill effects. These observations have been addressed in the following sections.

**Mint Protects against the Radiation-Induced Hemopoietic Syndrome**

The lymphohematopoietic elements are among the highly replicating tissues and are the most radiosensitive life-supporting organs.\cite{21} The oral administration of the aqueous extract of *M. piperita* as well as mint oil increased total erythrocyte and leucocytes counts, hemoglobin concentration, and hematocrit values.\cite{19,20} An increase in the number of bone marrow cells; the leucoblasts, myelocytes, metamyelocytes, band/stab forms, polymorphs, pronormoblasts, and normoblasts, lymphocytes, and megakaryocytes in bone marrow; and the levels of erythropoietin in serum were also observed at all the studied time points.\cite{19,20} The authors also observed a quantitative increase in the weight of the spleen and in the number of endogenous colonies (CFU-S). These observations suggest that the pretreatment with the mint extract protected the lymphohematopoietic elements from the deleterious effects of ionizing radiation, possibly through the free radical, antioxidant, and anti-inflammatory effects.\cite{19-21}
Mint Protects against the Radiation-Induced Gastrointestinal Syndrome

Ionizing radiation is rarely used to treat localized gastrointestinal (GI) tumors, and when obligatory is done with great caution and care. However, the GI tract is invariably exposed to scatter radiation when treating for cancer of the colon, rectum, prostate, and other closely linked sites. Samarth et al. studied the gastrointestinal protective effects of M. piperita in mice by evaluating the villus height, goblet cells/villus section, total cells, mitotic cells, and dead cells/crypt section in the mouse jejunum from day 1 to day 20 post-irradiation. The studies showed that administration of the aqueous extract of mint decreased the radiation-induced (8 Gy) alterations in intestinal mucosa of Swiss albino mice. Exposure to radiation alone caused a decrease in the villus height, number of total cells, and mitotic cells/crypt section with a concomitant increase in goblet cells and dead cells. Pretreatment with M. piperita reversed these changes, thereby indicating that it also possess enteroprotective effects.

Mint mitigates Radiation-Induced Behavioral Perturbations in Rats

Exposure to ionizing radiation causes a change in the behavioral perturbations such as emesis, conditioned taste aversion, performance decrement, learning and memory impairment. Radiation-induced conditioned taste aversion has been defined as a behavioral endpoint that is mediated by the toxic effects of radiation on the peripheral systems, primarily the gastrointestinal system.

Radiation causes aversion to the taste of saccharin in rodents. This is controlled by the same pathway(s) that control nausea and vomiting in man and shares many similarities with emesis. Due to these reasons the conditioned taste aversion has been proposed as a standard procedure and a reliable paradigm for evaluating behavioral alterations induced by radiation or other environmental agents/toxins.

Haksar et al. have observed that the oil from M. spicata mitigated the radiation-induced conditioned taste aversion in rats. Intraperitoneal administration of the oil before exposure to radiation offered significant radioprotection against conditioned taste aversion. Mint oil blocked the saccharin avoidance response within 5 post-treatment observational days and demonstrated that mint oil may be of use in preventing the radiation-induced behavioral changes.

Mint reduces the Radiation-Induced Testicular Damage in Mice

Testis is a radiosensitive organ and the degree and permanency of the damage depend on the treatment field, schedule of radiation, and the total received dose. The spermatogonia are the most radio-sensitive germ cells as exposure to a low dose of 0.1-0.2 Gy of ionizing radiation causes detectable changes, while at higher doses (>4 Gy) causes permanent azoospermia.

Recently, Samarth and Samarth investigated the protective effect of the aqueous extract of M. piperita against the radiation-induced testicular damage in mice by measuring biochemical parameters (lipid peroxidation, acid phosphatases, and alkaline phosphatases) and evaluating the histological alterations at various time points (days 1, 3, 7, 14, and 30 post-irradiation).

Exposure of animals to radiation alone caused a significant increase in the levels of lipid peroxidation and acid phosphatase activity at all available assay points (days 1 to 14). The histopathological results also supported the biochemical observations for massive damage to the various testicular cells. These observations clearly suggest the effectiveness of M. piperita in protecting against the deleterious effects of ionizing radiation.

Mechanism(S) of Action(S) [Figures 3 and 4]

Free radical scavenging

Dorman et al. evaluated the antioxidative properties of the aqueous extracts of various species of Mentha and observed that the M. x piperita “Frantsila” extract was better than the other extracts and that this activity was strongly associated with the phenolic content. The various fractionated extracts of the ethanolic extract of M. spicata were investigated using the 2,2’-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) decolorization assay. It was observed that the total antioxidant activity was highest in ethyl acetate and aqueous, and least in hexane and chloroform fractions. Correlation with the chemical analysis indicated that the antioxidant effects were again dependent on the phenolic content in the fractions.

The ethyl acetate, acetonitrile, and aqueous soluble extracts of M. piperita leaves were also observed to scavenge 1, 1’-diphenyl-2-picrylhydrazyl, 2,2’-azinobis(3-ethylbenzthiazoline-6-sulfonate) (DPPH), and hydroxyl radical scavenging assays; while the aqueous and dichloromethane-soluble extracts were effective in the β-carotene-linoleic acid bleaching inhibition assay. The essential oils from M. aquatica, M. longifolia, and M. piperita also possessed free radical scavenging effects and it was observed that the oil of M. piperita was effective in both DPPH and OH radical scavenging assays. The aqueous and chloroform extract of M. arvensis were potent scavengers of nitric oxide in vitro.

The polyphenolic compounds isolated from the aqueous...
extract of peppermint leaves, namely eriocitrin, luteolin-7-O-rutinoside, diosmin, hesperidin, narirutin, isorhamnetin, rosmarinic, and caffeic acids were studied for their antioxidant activity in the DPPH assay. The study showed that luteolin-7-O-rutinoside, eriocitrin, and rosmarinic acid possessed good activity, while caffeic acid, hesperidin, isorhamnetin, narirutin, and diosmin showed lesser activity. In the anti-H₂O₂ activity, good activity was observed for eriocitrin, rosmarinic acid, luteolin-7-O-rutinoside, and caffeic acid, while hesperidin, diosmin, narirutin, and isorhamnetin were not as effective. Independent studies also showed that monoterpenes ketones, menthone, and isomenthone were the most powerful scavenging compounds in the oil of M. longifolia and M. piperita, while 1,8-cineole in the oil of M. aquatica.

**Metal chelation activity**

The water-soluble extracts from the various species of Mentha were screened for their potential iron (III) reduction and iron (II) chelation effects. It was observed that M. aquatica, M. arvensis var. japonensis, M. x dalmatica, M. “Native Wilmet”, M. “Morocco”, and M. x Verticillata were better than M. spicata var. crispa, M. x piperita “Frantsila” and also that M. haplocalyx was better than the other extracts. The extracts of M. piperita with different polarities were also studied and it was observed that the petroleum ether, methanolic, and aqueous extracts demonstrated the best iron chelating activity. Both these reports suggest that mint possess iron chelating effects and that this may have partly contributed for the observed radioprotective effects.

**Mint possess Anti-mutagenic Effects and increases DNA Repair**

*In vitro* studies using S. typhimurium strains TA98 and TA1535 have shown that M. piperita was devoid of mutagenic effects. Additionally, mint is reported to be antimutagenic and to inhibit the mutagenity of the carcinogens/mutagens like benzo[a]-pyrene, aflatoxin B1, methylmethane sulfonate and extract of shamma, a complex mixture of powdered tobacco, slaked lime, ash, oils, spices and other additives, which has been linked to oral cancer in Saudi Arabia.

The phytochemicals linalool, eucalyptol, and myrcene present in mint are observed to prevent oxidant-induced genotoxicity and that this effect was mediated by their free radical scavenging activities. Luteolin is also reported to prevent the formation of strand breaks and protect PC12 cells against oxidative DNA damage. Emodin, another important constituent of Mentha inhibited the formation of 1-nitropyrene-induced DNA adducts in S. typhimurium TA98 in the ³²P-postlabeling study, indicating it blocks and/or suppresses the mutagenicity of 1-nitropyrene.

In association with the direct scavenging, blocking and/or suppressing mutagenic effects, Mint is also reported to enhance the error-free repair and this may also contribute to the antimutagenic activities. Niture et al. studied the alterations in O6-methylguanine-DNA methyltransferase (MGMT) activities of the water-soluble and alcohol-soluble constituents of spearMint (M. viridis) in human peripheral blood lymphocytes and cancer cell lines. Enhanced levels of MGMT effectively remove the highly mutagenic adducts formed by alkylating agents and the authors observed that the extracts marginally increased their levels and activities. Rosmarinic acid, an important constituent of mint, is also reported to increase the repair of oxidized nucleotidic bases induced by the photosensitizer [R]-1-[(10-chloro-4-oxo-3-phenyl-4H-benzo[a]quinolinizin-1-yl)carbonyl]-2-pyrrolidine-methanol (Ro 19-8022) by increasing expression of the OGG1 repair gene in PC12 cells.

**Mint protects against Radiation-Induced Clastogenicity**

Studies by Samarth et al. have shown that pretreatment with the aqueous extract of M. piperita decreased the radiation-induced chromatid breaks, chromosome breaks, centric rings, dicentrics, exchanges, and acentric fragments at all the time points studied. Concurrently, a quantitative decrease in...
the levels of micronucleus frequencies was also observed reinforcing the results of chromosomal aberrations for the anticlastogenic effects. All these studies clearly indicate that the observed antimutagenic, induction of DNA repair, and anticlastogenic effects of mint extract and by some of its compounds may have partly contributed to the observed radioprotective effects.

**ANTI-INFLAMMATORY ACTIVITY**

Studies have shown that *M. piperita* possesses an anti-inflammatory effect against both acute (xylene-induced ear oedema) and chronic (cotton-pellet granuloma) models of inflammation. The terpenoid oxide 1, 8-Cineole, present in mint, possess an inhibitory effect in carrageenan-induced inflammation and cotton pellet-induced granuloma in rats. Luteolin is also reported to inhibit arachidonic acid and 12-O-tetradecanoylphorbol-13-acetate-induced ear edema and oxazolone-induced allergic edema in mice.

**Mint decreases Radiation-Induced Lipid Peroxidation**

Aqueous extract of the various species of Mentha were tested for their ability to inhibit iron (III)-ascorbate-catalyzed hydroxyl radical-mediated brain phospholipid peroxidation in vitro. It was observed that the extract of *M. piperita* was better than the other extracts. Studies have also shown that the aqueous extract of *M. piperita* decreases the radiation-induced lipid peroxidation in the mice liver, blood, and testis.

**Mint restores Glutathione levels**

The oral administration of Mentha extract before exposure to γ radiation caused a significant increase in GSH content when compared to the radiation alone group on day 10 post-irradiation in the blood, liver, and testis of mice and contributed to the radioprotective effects.

**Mint increases Levels of Antioxidant Enzymes**

The pretreatment with the aqueous extract of *M. piperita* before exposure to 8 GY of γ radiation caused a significant increase in the activities of the antioxidant enzymes the superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase when evaluated 30 min post-irradiation.

**Mint reduces Serum Phosphatases**

Studies by Samarth *et al.* have shown that both oil as well as the aqueous extract of *M. piperita* modulated levels of serum phosphatases at different assay time points (6 h and 30 days post-irradiation). Exposure of Swiss albino mice to lethal dose of γ irradiation (8.0 Gy) caused a marked increase in the activities of serum phosphatas and acid phosphatase. Administering mentha oil (40 µl/animal/day) and aqueous extract (1 g/kg body wt) orally for 3 consecutive days prior to irradiation significantly decreased the levels of these enzymes. Further, the normal values were attained earlier than that for the radiation alone group.

**CONCLUSIONS**

Considerable information from pre-clinical studies suggests the usefulness of mint in preventing the toxic effects of ionizing radiation at non-toxic concentrations. While all studies have been with mice and validated mint’s clinical applicability to humans; *in vitro* studies with relevant propagatory cell lines and primary cultures will help in understanding the molecular mode of action responsible for the radioprotection.

Two independent encouraging observations have shown that both polar and non-polar fractions are effective in preventing radiation-induced sickness and lethality suggesting that mint contains both polar and non-polar compounds with radioprotective effects. Among the non-polar compounds it is quite possible that the antioxidant and anti-inflammatory compounds like menthol, eucalyptol, luteolin, β-myrcene, menthone, limonene, rosmarinic acid, and cineole may have been responsible for the observed effects. However experimental studies are needed to validate this. Among the water-soluble compounds, mint contains flavanoids like rutin, hesperidin, caffeic acid, carnosic acid, carnosol, and rosmarinic acid, which have all been reported to possess radioprotective effects. It is quite possible that the presence of these compounds in the aqueous extract might have contributed to the observed high DRF of the aqueous extract of mint.

Preliminary investigations by the author indicate that mint possess differential radioprotective effects in mammalian cells *in vitro*. However, further studies on determining the radioprotective activity of mint and its active components should be with tumor-bearing animals of different histological and metastatic potentialities, principally to observe for the normal tissue protection.

As most published radioprotective studies have been with
γ-radiation and Swiss albino mice, it is imperative that similar experiments are performed with other sources of ionizing radiations, especially the high LET sources and with other species of experimental animals as only then will the radioprotective spectrum be understood.

Studies should also be performed to understand whether in combination, mint could enhance the radioprotective effects of low doses of WR-2721 (< 500 mg/m² single dose and < 200 mg/m² for repeated administration) and also as to whether mint could prevent the systemic toxicity and delayed cytogenetic damage of the clinically used dose without impairing the protective efficiency. If mint is effective in enhancing the radioprotective effects of low doses or decrease the systemic toxicity and delayed cytogenetic damage (polyploidy and chromatid breaks) of high dose of WR-2721, it will be of immense help in clinics and will also reduce the treatment cost.

Apart from applications in the clinics, mint can be used as a radiation countermeasure in the management of radiological/nuclear incidents e.g., for the protection of defense personnel from nuclear weapon radiations; for protecting reactor workers and rescue crew; protection of astronauts from exposure to space radiation; protection of embryos against maternal exposure during pregnancy; protection against radiation-induced genomic instability, and radiation carcinogenesis. Human intervention trials as its effectiveness against as a radioprotective agent in occupational exposure and flight attendants must also be investigated.

Due to its abundance, low cost, and safety in consumption, mint remains a herb with tremendous potential and countless possibilities for further investigation. It has the potential to develop as a non-toxic radioprotective agent, but only when gaps in the existing knowledge are bridged.

ACKNOWLEDGEMENT

The authors wish to dedicate this article to Prof Ashok Kumar, Department of Zoology, Rajasthan University, Jaipur for his seminal studies on the radioprotective effects of Mentha piperita.

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Source of Support: Nil, Conflict of Interest: None declared.