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Assessment of the radioprotective effect of propolis in breast cancer patients undergoing radiotherapy. New perspective for an old honey bee product

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ABSTRACT

Background: Ionizing radiation is widely used for treatment of cancer. However, one of the limitations of using radiation is its toxic effects on normal tissue. Radiation damage to normal tissue can be partially reduced by the use of radio-protectors that scavenge free radicals produced during radiation. Recently, interest has increased in the development of potential drug of plant origin for the modification of radiation effects and has an advantage over the synthetic compounds in term of low or no toxicity and with minimum side effects. Propolis is apicultural product which is composed of nutritionally valuable substances and contains considerable amounts of polyphenol substances. Flavonoids and phenolic acids are the major classes of polyphenolic compounds. Because of its broad spectrum biological properties, the interest in propolis as harmless medicine has been increased.

Aim of the work: The present study has been undertaken to evaluate the radio-protective effect of propolis supplementation in breast cancer (BC) patients undergoing radiotherapy.

Subjects and methods: This study included 135 subjects divided into three main groups: Group I: 45 healthy females served as control group of matched age and menopausal status with the next malignant groups. Group II: 45 chemotherapy received breast cancer patients followed by radiation therapy only. Group III: 45 chemotherapy received breast cancer patients followed by radiation therapy plus propolis supplements. Two venous blood samples were collected from both breast cancer patients groups (Before and after radiotherapy) and one blood sample from matched controls. DNA damage in mononuclear cells was assessed by alkaline Comet assay. Serum was separated to measure ribonucleotide reductase M2 subunit (RRM2) by enzyme linked immunossorbent assay (ELISA). Malonaldhyde (MDA), total antioxidant capacity (TAC) and iron were assayed by colorimetric method. One ml blood sample was collected into EDTA tubes for complete blood picture analysis.

Results: The present study showed that radiotherapy is accompanied by significant increase in Comet tail parameters (Tail length, % Tail DNA, Tail moment) in peripheral blood

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mononuclear cells of BC patients. While in the group of patients supplemented with propolis plus radiotherapy, propolis have the ability to reduce significantly the radiation induced DNA damage. Concerning RRM2 subunit, it was found that, although radiotherapy significantly down regulate RRM2 protein but still significantly higher than normal control value. On the other hand, the supplementation of propolis during radiotherapy caused a significant down regulation of RRM2 level and became within the normal control level. Furthermore, radiotherapy is accompanied by significant increase in serum MDA and significant decrease in serum TAC while after propolis supplementation plus radiotherapy, serum MDA and serum TAC significantly improved. Regarding serum iron and hematological parameters including hemoglobin (HB) concentration, white blood cells (WBCs) and platelets counts were significantly decreased after radiotherapy treatment alone while after radiotherapy plus propolis, these parameters significantly increased and became within the normal control level.

Conclusions: Supplementation of propolis with radiotherapy treatment offers a quite measurable protection against DNA damage caused by ionizing radiation in BC patients leukocytes and inhibits RRM2 overexpression. Moreover, propolis has beneficial effects on the serum antioxidant capacity and improves the digestive utilization of iron and the regeneration efficiency of hemoglobin. Larger prospective studies are required to confirm our findings.

1. Introduction

Radiotherapy is the most common modality for treating human cancers. Eighty percent of cancer patients need radiotherapy at sometime or another, either for curative or palliative purpose (Paul, Unnikrishnan, & Nagappa, 2011). Radiation therapy destroys cells in the exposed area by damaging their genetic material (Sankaranarayanan, 2006). As radiation effects do not discriminate between normal and malignant cells and tissue, patients may experience symptoms during the course of therapy for a few weeks after therapy or months or years later (Karbownik & Reiter, 2000).

Several modalities and clinical approaches have been made to reduce these early and late complications of the radiotherapies and one among them is the use of an effective and non-toxic radio-protector (Kim, Seong, & Youn, 2006). Radioprotectors are compounds that are designed to reduce the damage in normal tissue caused by radiation. These compounds are often antioxidants and must be present before or at the time of radiation for their effectiveness (Maurya, Devasagayam, & Nair, 2006). To overcome harmful effects of synthetic compounds, many naturally occurring substances have been studied as candidates for effective radioprotection. These include polyphenols and honeybee products such as propolis. The awareness of their radio-protective properties has increased over the last decade, and their effects have extensively been studied in vitro and in vivo (Benkovic et al., 2009).

Propolis is adhesive resinous substance manufactured by honey bees from leaf, bud and sap of trees and flower blossoms. Major constituents of propolis are flavonoids, organic acids, phenols, various kinds of enzymes, vitamins and minerals (Bankova, 2005). Because of its broad spectrum of biological properties the interest in propolis as harmless medicine has been increased. Propolis and its active substances flavonoids showed antibacterial, analgesic/anti-inflammatory, antioxidant, immune-enhancement, anti-proliferative activity in cultured human tumor cells and anti-tumor activity in mice. Antioxidant activity of flavonoids is based on ability of direct free radicals scavenging or stabilizing the reactive oxygen species (ROS) by interacting with the reactive compound of the radical (Benković et al., 2008). Flavonoids can also increase the function of the endogenous antioxidant enzyme systems; superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase (Russo et al., 2000). Moreover, immune activity boosted by propolis and related compounds enhances haemopoietic regeneration and survival following radiation-induced lympho- and myelosupression (Oršolić et al., 2007). Reports of other authors confirm the protective effect of propolis on bone marrow and lymphoid tissue of mice treated with cytotoxic drugs (Lahouel, Boulkour, Segueni, & Fillastre, 2004; Sadzuka, Sugiyama, Shimoi, Kinae, & Hirota, 1997).

Several studies have demonstrated higher initial and/or residual DNA damage and lower repair rate following irradiation of peripheral blood lymphocytes (PBL) in vitro as compared to controls (Palyvoda, Polanska, Wygoda, & Rzeszowska-Wolny, 2003; Lou et al., 2007). Furthermore, many other studies have examined PBL of cancer patients who are undergoing chemotherapy or radiotherapy to see if the effect of radiation or anti-neoplastic drugs results in lymphocyte DNA damage in vivo; this approach is used as a surrogate indicator of how the tumor cells may be affected. These studies have shown that DNA damage is increased and/or DNA repair capacity is decreased in PBL samples from patients with a variety of cancers (Almeida, Duarte, Steward, & Jones, 2006; Nadin, Vargas-Roig, Drago, Ibarra, & Ciocca, 2006).

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