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REVIEW ARTICLE

Zingiber officinale Roscoe (ginger) as an adjuvant in cancer treatment: a review

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Summary

Despite acquiring a strong understanding of the molecular basis and advances in treatment, cancer is the second major cause of death in the world. In clinics, the stage-dependent treatment strategies may include surgery, radiotherapy and systemic treatments like hormonotherapy and chemotherapy, which are associated with side effects. The use of traditional herbal medicine in cancer patients is on a rise, as it is believed that these medications are non toxic and alleviate the symptoms of cancer, boost the immune system, or may tackle the cancer itself. Since antiquity the rhizome of Zingiber officinale Roscoe commonly known as ginger (family Zingiberaceae) have widely been used as a spice and condiment in different societies. Additionally, ginger also has a long history of medicinal use in various cultures for treating common colds, fever, to aid digestion, treat stomach upset, diarrhoea, nausea, rheumatic disorders, gastrointestinal complications and dizziness. Preclinical studies have also shown that ginger possesses chemopreventive and antineoplastic properties. It is also reported to be effective in ameliorating the side effects of γ-radiation and of doxorubicin and cisplatin; to inhibit the efflux of anticancer drugs by P-glycoprotein (P-gp) and to possess chemosensitizing effects in certain neoplastic cells in vitro and in vivo.

The objective of this review is to address observations on the role of ginger as adjuvant to treatment modalities of cancer. Emphasis is also placed on the drawbacks and on future directions for research that will have a consequential effect on cancer treatment and cure.

Key words: chemoprotective, chemosensitizers, Ginger rhizome, radioprotective, *Zingiber officinale*

Introduction

The high and widespread incidence of cancer is a leading health concern worldwide. Statistics suggest that in the year 2002, excluding the figures pertaining to non-melanoma skin cancers, over 10 million new cases of cancer were diagnosed with a death toll of nearly 7 million. It has been predicted that by the year 2020, there will be a rise in the incidence to 16 million new cases, with a death toll of 10 million and by 2030, over 20 million cases with 70% of the cancer deaths occurring in economically underdeveloped or developing countries, due to lack of treatment resources [1].

In a conventional setup, in most countries surgery, chemotherapy and radiotherapy are the three commonly used treatment modalities for treating cancer. Depending on the stage of the tumor, its localization and general health of the patient these modalities may be used individually or combined [2]. When a tumor is benign and operable, surgery is the treatment of choice. However, when a tumor is benign and inoperable, as with the case of a deep seated brain tumor, radiotherapy is preferred [3].

In the case of metastatic cancer chemotherapy is obligatory. Cancer chemotherapy may consist of a single drug or combinations of drugs [2]. Chemotherapy is also used in juxtaposition with surgery and radiotherapy with an aim to kill the residual neoplastic cells in the localized area, enhance the cytotoxic effects of ionizing radiation and also destroy neoplastic cells that may have metastasized from the primary site [4,5]. Estimates are that more than half of all people diagnosed with cancer receive chemotherapy [5].

Cytoprotectives in cancer treatments

Unlike surgery, treatment with both chemotherapy

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and radiotherapy are associated with mild to severe tissue reactions. The responses of immediate concern are those involving the hemopoietic and gastrointestinal cells, as they are highly sensitive and have life supporting functions. At times, the reactions can be significantly severe and may inevitably compel the physician to discontinue or reduce the dose of treatment, which will invariably diminish the effectiveness of treatment and ultimately the survival of the patient. Due to these limitations, there is an urgent need for improved therapeutics which are selectively cytotoxic to the preneoplastic and neoplastic cells or to develop radioprotective / cytoprotective agents against radiation and chemotherapeutic agents that may preferentially protect the normal cells from the cytotoxic effects or chemosensitizers / radiation sensitizers that will selectively enhance the effect [2,4].

Numerous studies have demonstrated that the sulfur-containing nucleophiles amifostine [(S-2-(3-aminopropylamino)-ethyl phosphorothioic acid)] also known as WR-2721 (Walter Reed 2721) (ethiofos, ethanethiol, ethyol and ethois) and mesna [2-Mercaptoethane sulfonate], and dexrazoxane [ADR-529, ICRF-187, (+)-(S)-4,4'-(Propane-1,2-diyl)bis(piperazine-2,6-dione) to be of use as chemoprotective agents and are administered shortly before chemotherapy or radiotherapy [6]. Similarly the synthetic chemicals like metronidazole (2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol), Elacridar (N-[4-[2-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)ethyl]phenyl]-5-methoxy-9-oxo-10H-acridine-4-carboxamide), Tariquidar (*N*-[2-[[4-[2-(6,7-Dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl] phenyl]carbamoyl]-4,5-dimethoxyphenyl] quinoline-3-carboxamide), Zosuquidar ((2*R*)-1-{4-[(1a*R*,10b*S*)-1,1-difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*] cyclopropa[*c*][7]annulen-6-yl}-3-(quinolin-5-yloxy) propan-2-ol), thio semicarbazone (3-aminopyridine-2-carbaldehyde thiosemicarbazone), verapamil (*RS*)-2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl]-(methyl)amino}-2-prop-2-yl pentane nitrile), nifedipine (3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) and trifluoperazine (10-[3-(4-methylpiperazin-1-yl) propyl]-2-(trifluoromethyl) -10*H*-phenothiazine) might sensitize tumor cells to radiation or anticancer drugs even in drug resistant neoplastic cells [7,8].

Unfortunately, applications of both synthetic protective and sensitizing compounds have been less than hoped for, owing to their highly selective organotropic effects and untoward toxicity [9]. Thus, the search to identify or develop less toxic or non-toxic broad spectrum chemoprotective or chemosensitizing agents still remains an area of priority [7,9] and emphasis is being laid on natural products as these ingredients are regularly used in daily diets in one form or another and may be easily accepted by humans [10].

To be of use in clinics, the protective or sensitizing agents should ideally possess high degree of protection to the normal cells and not to the neoplastic cells; ought to be easily absorbed by normal tissues, metabolized and eliminated; offer long term protection to different organs of the body but more importantly to the gastrointestinal, hematopoietic, pulmonary, nervous and vascular systems; should be non-toxic at the optimal protective concentrations; should be devoid of systemic toxicity, reproductive toxicity, genotoxicity or teratogenicity; effective in more than one species of animal; easy to administer and preferably through oral route; affordable to patients at low cost and possess acceptable shelf life [3,7,9,11].

The herbal drugs offer an alternative to the synthetic compounds and are considered either non-toxic or less toxic than their synthetic counterparts. In the recent past, plants and some phytochemicals with free radical scavenging, antioxidant properties, metal chelating effects and immunostimulatory effects have been evaluated for their chemoprotective effects in different experimental systems [10].

Ginger, the rhizomes of *Zingiber officinale* Roscoe (*Zingiberaceae*) (Figure 1), has widely been used as a spice and condiment in different societies. Besides its food-additive functions, ginger has a long history of medicinal use for the treatment of a variety of human ailments. In Sanskrit, ginger is known as Sringavera and it is speculated that this term may have given way to Zingiberi in Greek and then to the Latin term Zingiber [12]. Ginger is supposed to have originated in the South-East Asia (today's Northeast India) and has been cultivated for thousands of years as a spice and also for medicinal purposes [13]. Laboratory studies have also shown that ginger possesses free radical scavenging, antioxidative, anti-inflammatory, antimicrobial, antiviral, gastroprotective, antidiabetic, anti-hypertensive, cardioprotective, anticancer, and immunomodulatory effects [14-16]. Animal studies have demonstrated effects on the gastrointestinal tract, the cardiovascular system, on experimental pain and fever, antioxidative, antilipidemic and antitumor effects [15,16].

Ginger contains several phytochemicals which account for many of its health beneficial effects. The most important compounds responsible for Ginger's therapeutic activity are grouped into non-volatile and volatile compounds. The non-volatile fraction consists of an oleoresin (4.0-7.5%). When extraction with dissolvent is performed on this fraction, pungent elements, non-pungent elements and an essential oil fraction are ob-

Figure 1. Photograph of a Zingiber officinale Roscoe plant with the rhizome.

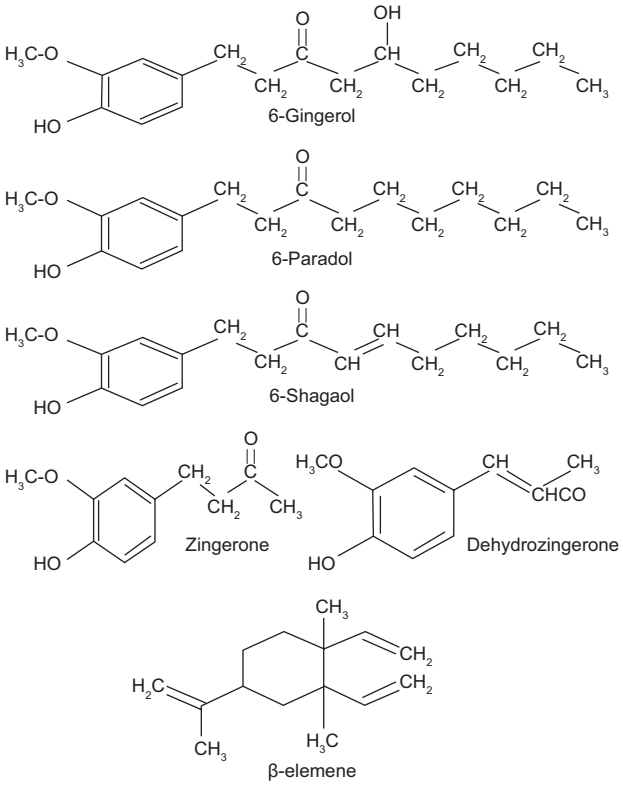

Figure 2. Structures of some phytochemicals present in the ginger rhizome.

tained. Those elements responsible for Ginger's spicy flavor and partly responsible for its numerous beneficial actions have been identified as 1-(3'-methoxy-4'-hydroxyphenyl)-5-hydroxyalkan-3-ones, also known as the *Gingerols* group, which bear a lateral chain of variable length. In relation to these chains, the isolated and identified *Gingerols* have been named [3]-, [4]-, [5]-, [6]-, [8] - and [10]-Gingerol. More pungent but present in lower concentrations are the shogaols (phenylalkanones), products coming from dehydration of Gingerol, whose concentration increases during the drying process and the storing. Phytochemical studies have shown that [6]-Gingerol and [6]-shogaol are found in greater concentrations (Figure 2). Other pungent elements, though present in lower proportion, are gingediols, gingediacetates, gingerdione and gingerenones, dehydrozingerone (Figure 2) and zingerone (Figure 2) [12,17,18].

The composition of the volatile fraction consists mainly of the *sesquiterpene* derivatives (>50%), responsible for the aroma, whose concentration seems to keep constant. Such compounds include (-)-zingiberene (20-30%), (+)-ar-curcumene (6-19%), (-)-β-sesquiphelandrene (7-12%) and β-bisabolene (Figure 2) (5-12%). The monoterpene derivatives are also a part of this essential oil, though in lower proportion. Among the characteristic of ginger that have been isolated, we can mention α-pinene, bornyl acetate, borneol, camphene, ρ-cymene, cineol, citral, cumene, β-elemene, farnesene, β-phelandrene, geraniol, limonene, linalol, myrcene, β-pinene and sabinene [12,17,18].

Studies in the recent past have shown that the ginger rhizome is effective in ameliorating the side effects of γ-radiation and the anticancer drugs doxorubicin and cisplatin [21-26]. Since antiquity, ginger has been documented to be effective as an anti-emetic drug and some studies have extended this observation into the prevention of anticancer treatment-induced nausea [15]. Further preclinical studies with relevant *in vitro* systems of studies have shown that ginger inhibits the multidrug resistance (MDR) efflux of anticancer drugs, thereby being of additional use. In the current review all these aspects are addressed with emphasis on the future directions.

Preventing radiation toxicity

Since the discovery of the deleterious effects of ionizing radiation, studies have been focused on developing chemical radioprotectors that have ability to de-

crease the biological effects of radiation on normal tissues, lethality, mutagenicity and carcinogenicity [27]. Albeit numerous compounds with diverse chemical structures and pharmacological properties have been studied very few compounds have been of use in clinics [10]. The thiol compound amifostine is credited of being the only radioprotector to have been approved by FDA to reduce the incidence and severity of xerostomia in head and neck cancer patients undergoing radiotherapy. Unfortunately, the application of this drug has so far been less than hoped for, owing to untoward toxicity often being evidenced at optimal radioprotective doses [27].

With regard to ginger, studies by Jagetia et al. [19,20] have reported that the hydroalcoholic extract of ginger was effective in preventing the γ-radiation induced sickness and mortality both when administered intraperitoneally (i.p.) and orally [19,20]. When administered i.p., of all the doses tested (5, 10, 20 and 40 mg/kg b.wt), the extract at 10 mg/kg for 5 consecutive days (total of 50 mg/ kg b.wt) was most effective in increasing mouse survival and also that a single i.p. dose of 50 mg, or 25 mg once daily for 2 days were ineffective [19].

The dose reduction factor (DRF) was 1.15 and the optimum protective dose of 10 mg/kg ginger extract was 1⁄50 of the LD_{50} (500 mg/kg) suggesting it to be safe and devoid of drug toxicity [19]. When administered orally for 5 consecutive days, the same extract was observed to be most effective at 250 mg/kg b.wt and caused a DRF of 1.2, suggestive of its effectiveness in both routes and also that a 25- fold increase in the concentration was required when the extract was administered orally [20].

Lessons from the experience with radioprotectors are that animal studies with survival as the endpoint are the most confirmatory, as in rodents, death within 10 days post-irradiation is due to gastrointestinal epithelial damage while death from 11 to 30 days is due to h*ematopoietic* damage [19,20]. The results of these experiments confirmed the radioprotective effects of the ginger extract and its possible utility as a non toxic radioprotector. Studies have also shown that two ginger phytochemicals, dehydrozingerone and zingerone, also possess radioprotective effects [28,29]. A single i.p. administration of 100 mg/kg of dehydrozingerone and the oral administration of 20 mg/kg b.wt zingerone for 5 consecutive days before exposure to supralethal dose of 10 Gy of the γ-radiation offered the best protection. The DRF was calculated and observed to be 1.1 and 1.2 respectively, for dehydrozingerone and zingerone [28,29].

Both compounds maintained the spleen index and stimulated the endogenous spleen colony forming units (CFU), reduced the radiation-induced DNA damage as evaluated by the bone marrow micronuclei in mice bone marrow, protected the gastrointestinal tract and increased the crypt cells proliferation and regeneration [28,29]. Mechanistic studies showed that the hydroalcoholic extract of ginger (dehydrozingerone and zingerone) was an effective scavenger of free radicals, inhibited the formation of radiation-induced lipid peroxidation with a concurrent increase in the levels of the antioxidant glutathione and the antioxidant enzymes, and prevented radiation-induced DNA damage [14,19-22,28-30] (Figure 3). Recently, zingerone is reported to inhibit radiation-induced apoptosis of V79 cells by inhibiting the activation of caspase-3, by upregulating Bcl-2 and down-regulating Bax proteins [30]. All these mechanisms may have contributed for the observed radioprotective effects.

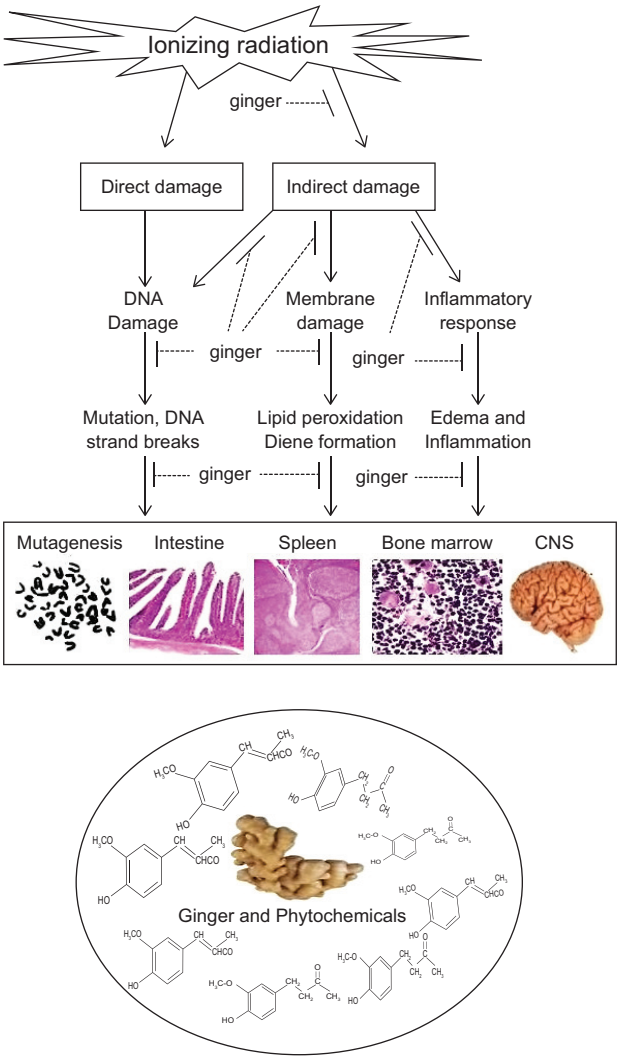

Figure 3. Schematic diagram indicating the mechanisms responsible for the radioprotective effects of ginger and its active compounds zingerone and dehydrozingerone.

Chemoprotective effects

Since their approval for clinical use by the FDA in the 1970s, the antineoplastic drugs doxorubicin and cisplatin have had a major positive effect in cancer treatment and patient survival. While doxorubicin is preferred in the treatment of Hodgkin's lymphoma, breast cancer, small cell lung cancer, soft tissue sarcoma, multiple myeloma and recurring cases of ovarian cancer, cisplatin is used in the treatment of testicular, ovarian, bladder, head and neck, esophageal, small and non-small cell lung, breast, cervical, stomach, and prostate cancers, neuroblastoma, sarcomas, multiple myeloma, melanoma, mesothelioma, Hodgkin's and non-Hodgkin's lymphomas. Both drugs are also reported to be teratogenic, mutagenic and reproductive toxicant [4].

These drugs have a steep dose-response curve for both antitumor and the early adverse effects, which include nausea, vomiting, myelotoxicity, loss of appetite, tiredness, weakness and diarrhea. These side effects are of immediate concern and may limit the use of the treatment dose. Further, the clinical use of high doses of these cytotoxic agents are limited as both radiation and cancer chemotherapeutic drugs cause long-term damage. Cisplatin is observed to cause irreversible renal dysfunction, ototoxicity and neuropathy, while doxorubicin principally causes cardiotoxicity that can lead to irreversible congestive heart failure; nephrotoxicity has also been reported [4].

The aqueous ethanol extract of ginger rhizome has been observed to protect rats against the doxorubicin-induced nephrotoxicity [26]. Administration of doxorubicin alone (15 mg/kg i.p.) caused a marked increase in the levels of serum urea and creatinine levels. In the kidneys of these animals the levels of reduced glutathione, the enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase activities were significantly decreased with a concomitant increase in the levels of lipid peroxidation [26].

Administration of the ginger extract (200 and 400 mg/kg) prior to doxorubicin decreased the serum urea and creatinine levels, suggesting a protective effect against the doxorubicin-induced nephrotoxicity. The levels of lipid peroxides were also decreased and there was an associated increase in the levels of the renal antioxidant enzymes in the ginger plus doxorubicin treated group [26]. The nephroprotective effect of 400 mg/kg of ginger was observed to be better than 200 mg/kg b.wt of Vit E used as positive control [26]. Taken together, these results indicate that ginger protects both heart and kidneys against the deleterious effects of single administration of doxorubicin [26].

Ginger at 250 and 500 mg/kg b.wt also protected mice against cisplatin-induced nephrotoxicity. When compared with the cisplatin alone treated group, oral feeding of ginger before and after cisplatin administration caused a dose-dependent decrease in the serum levels of creatinine, urea and in lipid peroxides in the kidneys, with a concomitant increase in the levels of renal antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase activities, and in free glutathione levels [25]. The effects of both concentrations of ginger were better than that of Vit E and combining ginger (250 mg/kg) with Vit E (250 mg/kg) further increased the nephroprotective consequence [25]. These studies also emphasized that the nephroprotective effects of ginger against two different toxic agents were mediated through the antioxidant defense system or by their direct free radical scavenging activity [25,26].

Studies have shown that 6-gingerol also possesses nephroprotective effects against the cisplatin-induced oxidative stress and renal dysfunction. 6-gingerol in dosages of 12.5, 25, 50 mg/kg when administered 2 days before and 3 days after cisplatin administration restored renal function as assessed by measuring serum creatinine, blood urea nitrogen, creatinine clearance and serum nitrite levels; it also reduced lipid peroxidation and enhanced the levels of reduced glutathione and activities of superoxide dismutase and catalase. All these suggested that 6-gingerol has a potential to be used as therapeutic adjuvant in cisplatin nephrotoxicity [31].

Apart from nephrotoxicity, cisplatin causes testicular damage both in spermatogenesis and testicular endocrine functions in humans and rodents. Damage of the testicular germinal epithelium, which may be transient or permanent, is of particular concern in case of men of reproductive age having germ-cell tumors with high cure rates. In rodents, within days of cisplatin injection, animals show severe testicular damage, which is characterized by spermatogenic damage, germ cell apoptosis, Leydig cell dysfunction and testicular steroidogenic disorders [32].

Administration of the ethanolic extract of ginger protected rats from cisplatin-induced testicular toxicity by increasing the activities of testicular antioxidant enzymes (Figure 4). Ginger administration decreased sperm abnormality, enhanced the sperm motility and restored the testis morphology by decreasing apoptotic cell death both in the testicular tissue and in the sperms [23,24]. The authors suggest that the protective effects of ginger may be due to the free radical scavenging and antioxidant effects of the ginger phytochemicals and also due to its potent androgenic activity in male rats, which may have resulted in increasing the testis weight and serum testosterone levels [23,33].

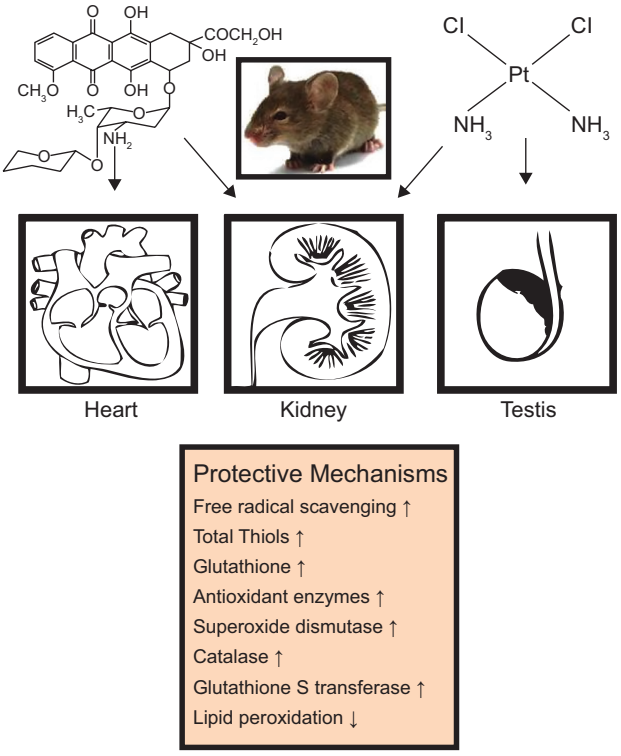

Figure 4. Ginger protects against the cisplatin-induced testicular toxicity and renal toxicity and doxorubicin-induced cardiotoxicity and nephrotoxicity by free radical scavenging and antioxidant effects.

Gingerol reversal of P-gp mediated multidrug resistance in some cancer cells *in vitro*

MDR, the principle mechanism by which many cancers develop resistance to chemotherapeutic drugs, is a major factor in the failure of many forms of chemotherapy. It affects patients with a variety of blood malignancies and solid tumors, including breast, ovarian, lung, and lower gastrointestinal tract cancers. Although multiple mechanisms mediate MDR, the most important is the one mediated by the P-gp, a product of MDR1, also referred to as ABCB1 gene [34]. P-gp mediates resistance to various classes of chemotherapeutic agents including vinblastine, vincristine, daunorubicin, doxorubicin, colchicine, paclitaxel, and etoposide, by actively extruding the drugs from the cells to lower the intracellular concentrations and is energy-dependent [35].

Studies have demonstrated that resistance mediated by P-gp may be modulated by a wide variety of compounds, including verapamil and cyclosporin A. These compounds have little or no effect on the tumor cells, but when used in conjunction with antineoplastic agents act to decrease, and in some instances eliminate drug resistance [34]. Nabekura et al. [35] investigated the effects of 6-gingerol on the function of P-gp in the human multidrug-resistant KB-C2 carcinoma cells. 6-gingerol increased the accumulation of daunorubicin in KB-C2 cells in a concentration-dependent manner. It also increased the accumulation of rhodamine 123 and decreased the efflux of rhodamine 123 from KB-C2 cells. 6-gingerol increased the cytotoxicity of vinblastine in KB-C2 cells [35]. Recently, Zhang and Lim [36] have also reported that 6-gingerol inhibited the P-gp-mediated [3H]digoxin transport in L-MDR1 and Caco-2 cells [36]. These results cumulatively suggest that 6-gingerol can partially reverse MDR in cells that express P-gp (Figure 5) and that it can become useful as an adjuvant to enhance the efficacy of cancer chemotherapy in treating chemorefractory cancers.

Chemosensitization by ginger phytochemicals in chemoresistant cells

With time, the treatment of cancer with chemotherapeutic agents can create a major problem in the form of chemoresistance and nonspecific toxicity toward normal cells. Studies suggest that modulating the drug sensitivity with chemosensitizers can be fruitful, as it causes "resistance modification", a strategy effective in treating some tumors with intrinsic or acquired drug resistance [7]. Recent studies have suggested that some plant polyphenols like genistein, curcumin, resveratrol, silymarin, caffeic acid phenethyl ester, flavopiridol, emodin, green tea polyphenols, piperine, oleandrin, ursolic acid, and betulinic acid might be of use to sensitize tumor cells to chemotherapeutic agents at pharmacologically safe concentrations by inhibiting pathways that lead to treatment resistance [8].

Studies have shown that β-elemene, a phyto-

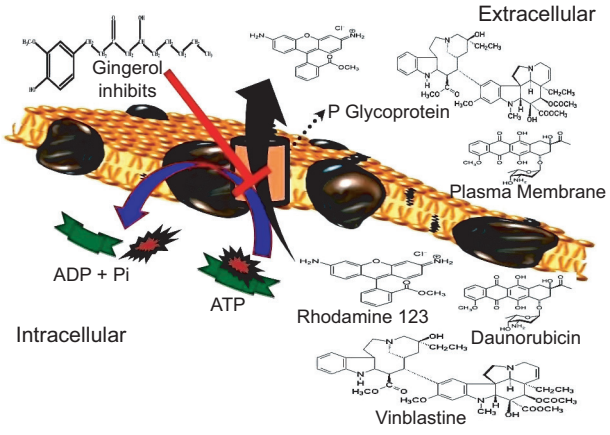

Figure 5. Ginger constituent 6 - gingerol reverses the P-glycoprotein mediated efflux of the antineoplastic drug and study compound rhodamine 123.

chemical present in high concentration in the *Rhizoma zedoariae* or *Curcuma* zedoaria Roscoe and in traces in ginger, inhibited the proliferation of the cisplatin-resistant human ovarian cancer cells and their parental cells, without affecting the normal human ovarian cells. It was also observed that β-elemene also sensitizes chemoresistant ovarian carcinoma cells to cisplatin-induced growth suppression, partly through modulating the cell cycle G2 checkpoint and inducing cell cycle G2-M arrest, downregulating the cyclin B1 and Cdc2 expression, but elevating the levels of p53, p21waf1/cip1, p27kip1 and Gadd45, and increasing the phosphorylation of Cdc2 and Cdc25C, which concomitantly causes a reduction in Cdc2-cyclin B1 activity which ultimately lead to blockade of cell cycle progression and cell death [37].

The combination of β-elemene and cisplatin caused a synergistic tumoricidal effect on, Hep-2 laryngeal carcinoma cells *in vitro* and *in vivo* (xenograft growth in nude mice) [38,39]. Recently, Li et al. [40] have also observed that β-elemene sensitizes the human non-small cell lung cancer cell lines H460 and A549 to cisplatin. β-elemene considerably enhanced the inhibitory effect of cisplatin on cell proliferation in a time- and dose-dependent manner [40].

The combination enhanced apoptosis and was mediated through the mitochondria-mediated intrinsic apoptosis pathway involving Bcl-2 family proteins and IAPs. β-elemene is observed to enhance caspase-3 activity, and thus inhibits protein expression of eIFs (4E, 4G), bFGF, and VEGF. *In vivo*, the growth of Hep-2 cell-transplanted tumors in nude mice was inhibited by intraperitoneal injection of β-elemene [40]. Compared with control groups, β-elemene significantly inhibited the protein expression of eIFs (4E and 4G), bFGF, and VEGF and decreased the microvessel density. The anticancer effects of β-elemene are associated with the inhibition of bFGF and VEGF mediated angiogenesis and is closely associated with alterations in the expression of eIF4E and eIF4G. Together these observations provide a rationale for developing a combination of β-elemene and cisplatin as a regimen for the treatment of refractory tumors [40].

Antiemetic property of ginger against chemotherapy and radiation-induced emesis

Nausea and vomiting can cause considerable distress and discomfort to patients undergoing chemotherapy, radiotherapy, or surgery. Severe nausea and vomiting can result in dehydration, electrolyte imbalance, metabolic disturbances, and aspiration pneumonia, which can have substantial effects on quality of life, survival, and health care costs. Treatments used to control nausea and vomiting form a critical part of the supportive care of cancer patients and should not, therefore, add to the patient's side-effect burden [41].

Ginger has been used for medicinal purposes since antiquity and one of its specific uses has been the treatment of nausea and vomiting. Several lines of scientific evidence support the beneficial effects of ginger on nausea and vomiting associated with motion sickness, surgery, and pregnancy [42]. Preclinical studies by Sharma et al. [43] for the first time examined the antiemetic effects of acetone, 50% ethanolic and aqueous extract against cisplatin-induced emesis in healthy mongrel dogs. The oral administration of acetone and hydroalcoholic extract at doses of 25, 50, 100 and 200 mg/kg b.wt exhibited significant protection. Of the two, the acetone extract was more effective than the ethanolic extract, but both were less effective when compared to the 5-HT3 receptor antagonist granisetron. The aqueous extracts at the same concentrations were ineffective, suggesting that the non polar compounds of the extract to be responsible for the antiemetic effects [43].

The acetone and 50% ethanolic extract of ginger at doses of 100, 200 and 500 mg/kg as well as the fresh ginger juice at doses of 2 and 4 ml/kg were also effective in inhibiting the cisplatin-induced gastric emptying in rats. All three ginger preparations significantly reversed the cisplatin-induced delay in gastric emptying. The acetone extract was similar to ondansetron in its effect [43]. Ginger juice produced the best reversal and was better than that of the 5-HT3 receptor antagonist ondansetron, while the effect of acetone extract was similar to that caused by ondansetron [44].

Studies have also shown that the hydroalcoholic extract of ginger mitigated γ-radiation-induced conditioned taste aversion in Sprague-Dawley rats and that the extract was comparable to the antiemetic drugs ondansetron and dexamethasone in its efficacy [21,22]. The dose of 200 mg/kg b.wt. was effective for males while for female rats it was at 250 mg/kg b.wt, clearly indicating that the male and female rats may respond differentially towards radiation exposure in relation to the conditioned taste aversion and also that ginger extract optimally acts at different concentrations in both sexes [22].

The oral administration of 6-gingerol completely prevented cyclophosphamide-induced vomiting in response in house musk shrew (*Suncus murinus*), presumably via a central effect [45]. Recently, gingerol is also reported to have decreased the frequency of cisplatin-induced retching and vomiting in the mink model of vomiting [46]. When compared with the cisplatin-alone group, gingerol caused a dose-dependent decrease in the

levels of 5-HT3 and dopamine (DA) levels in the area postrema and ileum. It also suppressed the increase in the immunoreactivity of substance P induced by cisplatin in the mucosa and submucosa of ileum, as well as in the neurons of the area postrema. All these results suggest that gingerol has good activity against cisplatin-induced emesis in minks and does so by inhibiting the central or peripheral increase of 5-hydroxytryptamine, dopamine and substance P [46].

The exact mechanism responsible for the antiemetic effects of ginger is unknown. However, seminal studies by Abdel-Aziz et al. [47] suggest that the ginger phytochemicals (6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol) may function as a 5-HT3 antagonist, neurokinin-I receptor (NKI) antagonist, antihistaminic and prokinetic effects. The authors suggest that these phytochemicals exert their antiemetic effect at least in part by acting on the 5-HT3 receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin binding site and also that this may include the indirect effects via receptors in the signal cascade behind the 5-HT3 receptor channel complex such as substance P receptors and muscarinic receptors [47] (Figures 6,7).

However, despite the enthusiastic observations for its antiemetic properties in animals, contradictory results have been observed from the limited human studies with ginger. In one of the earliest studies Pace [48] investigated the antiemetic effect of ginger in leukemic patients receiving chemotherapy. The patients were randomized to receive oral ginger or placebo in addition to prochlorperazine. The results showed that when compared to those receiving placebo, a significant reduction in nausea was observed in patients receiving ginger [48].

Studies by Meyer et al. [49] and Pecoraro et al. [50] have also supported ginger's use as an antiemetic in patients undergoing chemotherapy. Additionally, experiments have confirmed that ginger is also effective in reducing nausea and vomiting induced by low dose cyclophosphamide in combination with other anticancer drugs causing mild emesis [51]. However, the antiemetic efficacy of ginger was found to be equal to that of metoclopramide but inferior to that of ondansetron [51].

In a double-blind crossover study, Manusirivithaya et al. [52] observed that the addition of ginger to standard antiemetic regimen of gynecologic oncology patients receiving cisplatin offered no advantage in reducing nausea or vomiting in acute phase of cisplatin-induced emesis, while in the delayed phase it was effective and that the beneficial effect was comparable to that of metoclopramide [52]. The addition of ginger to standard antiemetic medication further reduced the severity of post chemotherapy-induced nausea in cancer patients [53]. Further, consumption of high protein meals with ginger also reduced the delayed nausea of chemotherapy and decreased the use of antiemetic medications [42].

Studies have also shown that the administration of ginger (0.5, 1.0 or 1.5 g) along with 5-HT3 receptor antagonists reduced the chemotherapy-induced nausea in patients undergoing treatment for breast, alimentary and lung cancers [54]. The optimal effect was observed for the cohorts who had received 0.5 or 1.0 g of ginger [54].

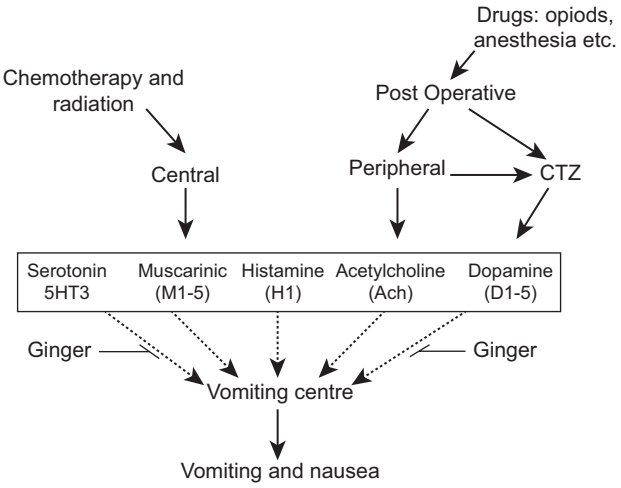

Figure 6. Mechanistic representation of the antiemetic effects of ginger.

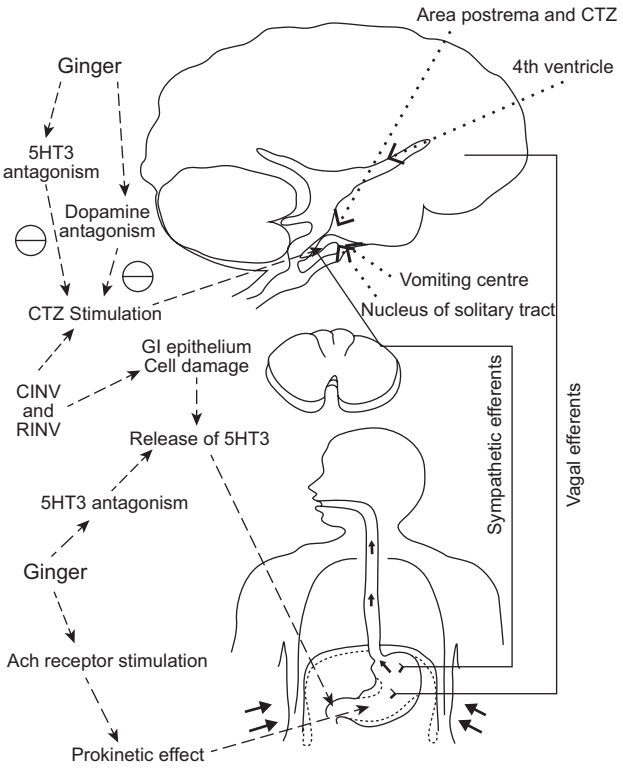

Figure 7. Mechanisms responsible for the prevention of CINV in ginger. ⊖ = inhibition.

Very recently, Pillai et al. [55] have also observed that ginger root powder was effective in reducing the severity of acute and delayed chemotherapy induced nausea and vomiting (CINV) when provided as a adjunct to ondansetron and dexamethasone in bone sarcoma patients receiving highly emetogenic chemotherapy containing cisplatin/doxorubicin. Together these reports clearly suggest the usefulness of ginger as an adjuvant to the conventional antiemetic agents.

Conversely, contradictory observations have emerged from some clinical studies, which report that ginger does not provide any additional benefit for reduction of the prevalence or severity of acute or delayed chemotherapy-induced nausea and vomiting when given alone or with 5-HT3 receptor antagonists and/or aprepitant [52,56].

Future directions

Studies in the recent past have brought the cytoprotective effects of ginger and some of its bioactive components into the limelight. With regard to its chemoprotective and radioprotective properties, an array of mechanisms including free radical scavenging, anti-inflammatory effects, antioxidant and antimutagenic activities are thought to be responsible for the beneficial effects. Studies focused on understanding the selective protection with tumor-bearing animals will help realize the clinical utility of it as a selective radioprotective and chemoprotective drug against the deleterious effects of ionizing radiation and anticancer agents cisplatin and doxorubicin.

As ginger is a dietary agent with vast acceptance, in addition to its use as a possible radioprotective agent in cancer treatment, it can be of use as antioxidant radioprotective agent for non clinical purposes, where exposure to ionizing radiation is a possibility like in occupational exposures, radiation site clean-up, radiological terrorism and in military scenarios. Furthermore, the usefulness of a nontoxic radioprotective agent is applicable not only for the treatment of cancer but also for space-flight professionals and airplane passengers since high altitude flights expose humans to hazardous cosmic rays. Use of ginger as dietary radioprotective may be highly successful for humans as use of natural products would not put an extra burden on the body and ginger also possesses other beneficial health effects.

The observations that gingerol reverses the P-gp mediated anticancer drug efflux is of additional significance. In cancer treatment, chemotherapy kills drug-sensitive cells, but leaves behind a higher proportion of drug-resistant cells. As the tumor begins to grow again, chemotherapy may fail because the remaining tumor cells are now resistant. The observation that 6-gingerol inhibits the efflux can be considered as very promising as these phytochemicals can be used to reverse MDR in cancer.

The antiemetic property of ginger, especially in chemotherapy-induced nausea and vomiting, has been mixed. These discrepancies may be due to the difference in the ginger used in these studies. The phytochemicals gingerols, paradols and shogoals are key to the pharmacological properties of ginger and studies have shown that their pharmacokinetics vary significantly. The concentration of these compounds varies from place to place and the way in which the ginger has been processed post harvesting. The lead compound of raw ginger, gingerol is thermally labile and converts to the corresponding shogoals upon dehydration [57]. It is logical to assume that the divergent observations in human studies may be due to the variance in chemical constituents in the ginger used in these studies.

Ginger's antiemetic effects are considered to be equivalent to that of metoclopramide, one of the lower ring antiemetics. Ginger's antiemetic effects are manifested even in motion sickness, postoperatively, and in pregnancy. Ginger is also reported to be effective in preventing nausea and vomiting after major gynecological surgery and also after gynecological laparoscopy at 6 hours post-operation [58-63]. Together, all these observations indicate the usefulness of ginger as an affordable interventional option in these conditions.

Conclusions

It is apt to say that ginger is a spice with an immense potential for further cancer therapeutic research owing to the ease of availability, low cost and safe consumption. With advanced research in the field of non toxic cytoprotection, ginger is undoubtedly a potential candidate. However, there still remains a lot to be unraveled, especially on issues related to whether the average consumption of dietary ginger is sufficient to show these cytoprotective effects; also the consequences, if any, of consumption of high concentrations of ginger, are yet to be addressed. On the other hand, an *in vitro - in vivo* correlation of the cytoprotective effect of ginger needs to be explored in more detail. It is a safer, affordable interventional option as a radioprotective, chemomodulator and antiemetic.

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