Ginger and Breast Cancer

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Cancer is one of the leading causes of death in the world, with breast cancer being the most prevalent cancer. Chemotherapy-induced nausea and vomiting (CINV) is one of the most serious side effects of chemotherapy. Because the current CINV treatment option has several flaws, alternative treatment options are required. Ginger has traditionally been used to treat nausea and vomiting, and it also has anticancer properties in breast cancer cells. Based on these findings, researchers investigated whether using ginger to treat CINV in breast cancer patients is both effective and safe.

ginger zingiber officinale breast cancer chemotherapy side-effect chemotherapy-induced nausea and vomiting

1. Introduction

Cancer is one of the leading causes of death in the world. According to cancer statistics in 2022, there are expected to be 1,918,030 new cancer cases and 609,360 cancer-related deaths [1]. Among them, breast cancer has the highest estimated new cases of 287,850 patients (31%) [1]. Chemotherapy, like other types of cancer treatment, is widely used in the treatment of breast cancer. Even though it is a necessary conventional treatment for cancer patients, it has a few serious side effects that can be fatal to cancer patients both during and after treatment and chemotherapy-induced nausea and vomiting (CINV) is one of them [2]. Chemotherapy for cancer patients is divided into four categories: high emetic risk, moderate emetic risk, low emetic risk, and minimal emetic risk [3]. Specifically, in comparison to cisplatin, melphalan, cyclophosphamide, and dacarbazine, which have a high emetogenic potential, anthracyclines, methotrexate, oxaliplatin, and carboplatin have a moderate emetogenic potential [3].

CINV is generally classified into five categories, which are acute, delayed, anticipatory, breakthrough, and refractory [4]. Acute CINV develops within 24 h of starting chemotherapy. Delayed CINV develops after 24 h of chemotherapy. Anticipatory CINV is a general response to chemotherapy. Despite appropriate prophylaxis, breakthrough CINV occurs within 5 days of chemotherapy, and refractory CINV occurs in subsequent chemotherapy cycles after the occurrence of breakthrough CINV in prior cycles, excluding anticipatory CINV [4]. Treatment agents for CINV and a combination of the agents are categorized as minimal, low, moderate, or high and the prevention and treatment strategies are varied depending on the severity of CINV [3]. Different types of treatments include dexamethasone which is a first-line use in combination with other agents [4]. However, side effects including insomnia, indigestion/epigastric discomfort, agitation, increased appetite, weight gain, and acne

were reported [5]. Untreated CINV is linked to treatment discontinuation, decreased quality of life, complications such as dehydration and electrolyte imbalances, and, ultimately, decreased treatment success and increased costs of care [5]. Therefore, efforts are being made to establish effective evidence-based clinical guidelines; for example, the ASCO (American Society for Clinical Oncology) has recognized acupuncture as an alternative therapy for CINV and is expected to provide additional alternative therapies as qualified evidence accumulates [6].

Ginger (Zingiber officinale) is a commonly used herb to treat nausea and vomiting, and several bioactive compounds, including shogaols, gingerols, zingerone, and paradols, have been identified within the ginger rhizome [7]. These compounds are thought to interact with a variety of areas involved in the development of CINV [8]. In cases of acute CINV, free radicals produced by toxic chemotherapy drugs stimulate enterochromaffin cells in the gastrointestinal tract, resulting in the production of serotonin [9][10]. Serotonin then binds to intestinal vagal afferent nerves via 5-HT_3 receptors, causing the vomiting reflex to be triggered in the CNS via the nucleus of the solitary tract (NTS) and chemoreceptor trigger zone (CTZ) [9][10]. Moreover, 5-HT_3 receptor signaling may be involved in delayed CINV, but to a lesser extent than in acute CINV [10]. Substance P is thought to be the main neurotransmitter involved in delayed CINV [11]. Chemotherapy drugs cause neurons in the central and peripheral nervous systems to release substance P, which then binds to neurokinin-1 (NK1) receptors, primarily in the NTS, to cause vomiting [10].

Ginger's bioactivity has been studied to see how it affects the CINV mechanism. Ymahara was the first to demonstrate that the whole ginger including gingerols 6,8 and 10 can inhibit 5-HT_3-induced contraction [12]. Followed by that, the 5-HT_3 antagonistic effect of ginger using four major compounds of ginger (gingerol 6,8,10 and 6-shogaol) was found in animal experiments [13]. Clinical trials for humans also reported that daily addition of ginger with conventional chemotherapy resulted in a favorable effect on CINV with no adverse effects [14][15][16].

Using ginger for breast cancer patients not only to treat CINV but also to manage the disease has numerous benefits. According to a study conducted in 2017 by Martin and his colleagues, 10-gingerol significantly inhibited metastasis of TNBC (Triple-negative breast cancer) cells dose-dependently [17]. Another investigation found that ginger therapy reduced colony formation and proliferation in MCF-7 and MDA-MB-231 breast cancer cell lines [18]. The non-tumorigenic normal mammary epithelial cell line (MCF-10A) was not severely affected by it, but there was a loss of cell viability, chromatin condensation, DNA fragmentation, activation of caspase 3, and cleavage of poly (ADP-ribose) polymerase. At the molecular level, the upregulation of the Bax and the downregulation of the Bcl-2 proteins may contribute to the apoptotic cell death caused by ginger [19].

2. Efficacy and Safety of Ginger on the Side Effects of Chemotherapy in Breast Cancer Patients

Nausea and vomiting caused by chemotherapy are both psychologically and physically distressing symptoms. Different treatment regimens are required for acute, delayed, anticipatory, breakthrough, and refractory CINV, which frequently include 5-HT_3 receptor antagonists, NK1 receptor antagonists, and corticosteroids [2][20]. Despite significant antiemetic agent research and development, CINV management remains a significant challenge, with

many unmet needs, such as controlling non-acute CINV, developing appropriate CINV treatment protocols for multiple-day chemotherapy patients, and providing options for those who are prone to CINV despite treatment [20]. Furthermore, common antiemetic drug side effects include headache, constipation, and fatigue [21].

As a result, there is an ongoing demand for complementary and alternative therapies. One of the most promising and actively researched options is herbal medicine. Ginger has been used to treat nausea and vomiting for over 2000 years [22]. Several clinical trials [16][23][24][25] have shown that ginger has an antiemetic effect against both the acute and delayed phases of CINV. Mechanisms of how ginger's components affect CINV are being researched. The main pungent constituents and fractions of ginger are 6-,8-,10-gingerol and 6-,8-,10-shogaol [26]. These components inhibit 5-HT_3 receptors in the central and peripheral nervous systems [27][28]. These receptors play an important role in the regulation of peristalsis, pain transmission, and nausea and vomiting. The development of 5-HT3 receptor antagonists improved the treatment of CINV in cancer patients significantly [27].

Various methods may be used to improve ginger accessibility for CINV patients. Ginger partitioned moxibustion may be more effective than no treatment in reducing the severity and frequency of CINV (RR: 2.04, 95% CI: 1.42–2.93); moxibustion may be more effective than antiemetic drugs (RR: 1.87, 95% CI: 1.27–2.76) [28]. Another study found that ginger moxibustion combined with acupuncture reduced gastro-intestinal tract reactions to chemotherapy in cancer patients when compared to a control group [29]. Ginger slice consumption and ginger-applied acupoint therapy were combined in Liu et al. (2020). All levels of CINV (mild, moderate, severe, and very severe) were assessed from 0 to 5 days after chemotherapy, and the severity of CINV between the two groups was significantly reduced ($p < 0.05$), implying that ginger could effectively manage CINV in breast cancer when combined with acupoint therapy [30]. Another study found that direct inhalation of ginger aromatherapy was beneficial [31].

Uncontrolled CINV reduces patients' quality of life (QOL), as well as their physical and social functioning. It can also result in medical complications such as poor nutrition, dehydration, and electrolyte imbalances [32]. It also leads to patients discontinuing potentially beneficial treatment regimens [32]. Uncontrolled CINV in a patient costs an extra USD 1300 per month in direct medical costs, according to one study [33]. However, current CINV treatments do not appear to be as effective as they could be [2]. Despite the existence of separate NCCN, ASOC, and MASCC/ESMO CINV practice guidelines, they share fundamental similarities and a lack of literature findings [6]. As a result, researchers determined that it was necessary to assemble evidence-based literature findings for CINV management, which could lead to the development of a new clinical practice guideline recommendation.

Although CINV can occur in any cancer patient receiving chemotherapy, researchers chose to focus on breast cancer patients for a number of reasons. First, ginger has been shown to be effective against breast cancer. Breast cancer is classified as either ER-positive (as in MCF-7 and T47D cell lines) or ER-negative (as in MDA-MB-231, MDA-MB-468, SKBR3 and MDA-MB-453 cell lines) [18]. Using additional biomarkers such as progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), breast cancer is further classified as luminal A, luminal B, basal-like, and HER2-positive [18]. Because these distinct subtypes of breast cancer respond differently to treatment, breast cancer is extremely difficult to treat. As a result, the search for complementary therapeutic

methods is ongoing. In MDA-MB-231 cells, for example, methanolic extract of ginger inhibited proliferation and colony formation in a dose- and time-dependent manner [34]. In MCF-7 and MDA-MB-231 cells, ginger extract increased Bax levels while decreasing Bcl-2 proteins, NF-B, Bcl-X, Mcl-1, survivin, cyclin D1, and CDK-4. Furthermore, ginger extract inhibited the expression of two important cancer molecular targets, c-Myc and hTERT [35]. Gingerols were discovered to inhibit breast cancer cell proliferation and metastasis. By inhibiting cyclin-dependent kinases and cyclins, 10-gingerol inhibited MDA-MB-231 proliferation, resulting in a G1 phase arrest [36]. Moreover, 10-gingerol also inhibited cancer cell invasion by inhibiting the activation of Akt and p38 (MAPK) [37]. Furthermore, 6-gingerol inhibited MDA-MB-231 cell migration and motility in a concentration-dependent manner, as well as MMP-2 and 9 expression and activity [38]. Shogaols also inhibited breast cancer cell metastasis via a variety of mechanisms, including MMP-9 inhibition of NF-kB activation, invasion of MDA-MB-231 cells, and inhibiting invasion by decreasing levels of c-Src kinase, cortactin, and MT1-MMP, all of which inhibited the growth and sustainability of breast cancer cells [39][40][41]. Furthermore, because the current meta-analysis on ginger's antiemetic effect on CINV focuses on all types of cancer and there is a lack of breast cancer focused analysis [42][43], researchers decided to focus on CINV in breast cancer patients for this entry based on previous research demonstrating ginger's anticancer effect in relieving CINV symptoms, as well as its beneficial effect on breast cancer itself, and the fact that breast cancer has the highest cancer prediction rate [1].

This meta-analysis included 337 patients from four randomized controlled trials, and researchers discovered that ginger was associated with a reduction in CINV (SMD −0.32, 95% CI −0.59, −0.05, $p = 0.02$; $I^2 = 75\%$). However, there was significant variation. As a result, researchers decided to conduct subgroup and sensitivity analysis. Subgroup analysis revealed that ginger was effective in reducing the severity of acute CINV in breast cancer patients (SMD −0.48, 95% CI −0.84, −0.13, $p = 0.008$; $I^2 = 66\%$). Another subgroup analysis of ginger's efficacy in acute vomiting revealed statistical significance (SMD −0.56, 95% CI −0.89, −0.22, $p = 0.001$; $I^2 = 0\%$). Ginger was also statistically significant in treating delayed CINV in breast cancer patients (SMD −0.48, 95%CI −0.82, −0.14, $p = 0.006$; $I^2 = 81\%$). There have been no serious adverse effects reported as a result of ginger consumption. Based on researchers' findings, researchers concluded that using ginger to treat CINV in breast cancer patients may be both effective and safe. However, because there were insufficient studies included in this analysis, evaluating publication bias using funnel plots was difficult. The sensitivity analysis comparing the fixed effect model and the random effect model yielded similar results. To advance the field and better inform clinicians and patients, more methodologically rigorous research on the safety and efficacy of ginger for CINV in breast cancer patients is required. CINV should be evaluated using validated tools for better meta-analysis. It must also be evaluated in terms of other side effects such as anxiety, depression, diarrhea, and quality of life as a result of chemotherapy.

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