Standardized ginger (*Zingiber officinale*) extract
as a treatment for chemotherapy-induced nausea
and vomiting: efficacy, safety and feasibility

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Abstract

Despite significant advances in anti-emetic therapy, chemotherapy-induced nausea and vomiting (CINV) remains a significant burden to cancer patients. Ginger (Zingiber officinale) has shown promise as an adjuvant to standard anti-emetic therapy to allay CINV. It contains several bioactive compounds that could interact beneficially with the multiple pathways involved in this adverse outcome of treatment. However, the results of previous clinical trials testing ginger are equivocal and the extant literature has multiple limitations that require further investigation.

The primary purpose of this Thesis by Publication is to determine the efficacy, safety, and feasibility of ginger in clinical practice through a systematic program of literature reviews, and clinical, survey, and laboratory studies that account for the limitations of the extant literature, and current gaps in the knowledge.

The aim of the first study undertaken in this thesis was to investigate the potential mechanisms of action exerted by ginger on CINV. Certain active compounds in ginger act via antagonism of the 5-HT3 receptors within the gastrointestinal tract leading to a possible reduction in CINV. Whether these compounds act directly at the serotonin binding site or act allosterically to modulate receptor activity has not been fully elucidated. Interactions between the principle compounds of ginger on the recently solved crystal structure of the murine 5-HT3 receptor were investigated using in silico techniques, in order to characterise the sites and determine if a preference in binding affinity is evident within the two distinct binding sites (Chapter 6). The results of this study demonstrated the investigated ginger compounds exhibited high binding affinity at both sites. We postulated that these compounds may potentially act at both
sites – as seen with other serotonin modulators. The observed binding promiscuity of these compounds is likely due to their high degree of non-covalent interaction potential.

The second study included in this thesis investigated the concentration of the primary bioactive compounds within 20 widely-available ginger products (including dietary supplements, beverages, and confectionary) using Reverse-Phase High-Performance Liquid Chromatography analysis (Chapter 7). This study addressed the efficacy and safety component of the projects aims by providing the following results. First, of the six dietary supplements analysed, standardized ginger extracts provided the most potent and consistent concentration of analysed ginger compounds, providing support for the use of standardized extracts in clinical trials. Second, when the concentration of compounds was presented by the approximate concentration that would be consumed in one serving, there were products from each product category that contained concentrations of the analysed compounds equal to, or exceeding, dietary supplements. This demonstrates that cancer patients could consume therapeutic concentrations of the active compounds within ginger through dietary intake alone. This has important implications for future clinical trials that aim to investigate the use of ginger supplementation. Furthermore, due to the potential effect ginger supplementation might exert on platelet aggregation, these results suggest that a high dietary intake of ginger products during chemotherapy could have safety implications. By analysing the concentration of primary compounds in a wide-range of commercially available ginger products, the information provided by this study will be able to inform Australian clinicians interested in these products for their adjuvant medicinal properties.
In the third and main study (Chapter 9), the efficacy and safety of ginger supplementation in humans was investigated in a clinical setting by way of a double-blind, randomized, placebo-controlled trial (N=51). This trial addressed the methodological limitations of the extant literature through the introduction of multiple robust features to the study design. These include following patients over an extended number of chemotherapy cycles, controlling for CINV-specific prognostic factors by recruiting only chemotherapy-naïve patients, implementing a dosing schedule consistent with the pharmacokinetics of oral ginger supplements, and independently analysing ginger supplements before and after the recruitment phase in order to ensure potency. The primary outcome was chemotherapy-induced nausea-related quality of life. Secondary outcomes included the severity, prevalence, and frequency of nausea, vomiting, and retching. This was also the first trial to assess the effect of ginger supplementation on cancer-related fatigue and nutritional status. The results of this study demonstrated a significant association between CINV- and nausea-related quality of life (p=0.043 and 0.029, respectively), global cancer-related quality of life (p=0.015), and cancer-related fatigue (p=0.007) in patients receiving the ginger intervention during the first cycle of chemotherapy. However, ginger supplementation did not reduce the prevalence or severity of CINV overall. There was no significant difference in reported adverse effects in the intervention group compared to the placebo group. By cycle 3 of chemotherapy, there was also significant attrition (33%). This suggests that the trial protocol could have been overly burdensome for participants and that the trial might not have been sufficiently powered to detect difference in CINV prevalence and severity. These results support previous studies, which indicate that ginger is well-tolerated; however, despite significant associations
between ginger supplementation and CINV-related quality of life (QoL), cancer-related QoL, and cancer-related fatigue, the use of ginger supplementation as an effective treatment for CINV is not supported by this trial.

The final study provided information regarding the feasibility of introducing dietary supplements such as ginger as a complement to routine clinical practice (Chapter 10). Healthcare professionals (N=370) responded to this survey, which assessed their current level of confidence, usage, and barriers with respect to recommending dietary supplements. The findings indicate mixed levels of confidence in recommending dietary supplements for their patients; nonetheless, there is strong interest in further training in this area despite the multiple barriers articulated, including concerns regarding drug-nutrient interactions.

In summary, the results of this thesis demonstrate that ginger supplementation is generally safe and feasible, and has several viable mechanisms of action related to CINV. While no reduction in the severity or prevalence of CINV were reported in our trial, ginger supplementation could be an effective and well-tolerated adjuvant intervention to enhance CINV-related QoL and reduce fatigue. Currently, healthcare professionals are interested in dietary supplements; however, further professional training in this area would improve the integration of dietary supplements into standard clinical practice. Future studies that explore the efficacy and the safety-profile of ginger are warranted in larger clinical trials.
Declaration

This thesis by publication is submitted to Bond University in fulfilment of the requirements of the degree of Doctor of Philosophy. This thesis represents my own original work towards this research degree and contains no material which has been previously submitted for a degree or diploma at this University or any other institution, except where due acknowledgement is made.
List of relevant publications and prizes

1.1 Relevant Peer-reviewed Publications


### 1.2 Publications submitted or in preparation


BioMed Central Alternative and Complementary Medicines. Impact factor: 2.02; Intended submission: December, 2015


1.3 Relevant Conference Abstracts and Presentations


1.4 Relevant Prizes and Awards

1. Best Poster Prize, MASCC/ISOO Symposium. Miami, USA (July, 2014)

2. Best Poster Prize, Nutrition Society of Australia Conference, Australia (November, 2014)

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List of abbreviations

Abbreviations included in this thesis are listed below.

5-HT3 – 5- Hydroxytryptamine

AA - Arachidonic acid

ADP - Adenosine diphosphate

CAM – Complementary and Alternative Medicine

CIN – Chemotherapy-induced Nausea

CINAHL - Cumulative Index to Nursing and Allied Health Literature

CINV – Chemotherapy-induced Nausea and Vomiting

CRF - Chemotherapy-Related Fatigue

CTZ – Chemotherapy Trigger Zone

ESAS - Edmonton Symptom Assessment System

FACIT-F - Functional Assessment of Cancer Therapy Fatigue

FACIT-F - Functional Assessment of Chronic Illness Therapies- Fatigue

FACT-G - Functional Assessment of Cancer Therapy- General

FLIE-5DR - The Functional Living Index – Emesis – 5 Day Recall

HEC, MEC, LEC – Highly/Moderately/Low Emetogenic Chemotherapy

HPLC – High Performance Liquid Chromatography

INR - International normalized ratio
INVR - Index of Nausea, Vomiting, and Retching

MANE – Morrow Assessment of Nausea and Emesis

MASCC - Multinational Association of Supportive Care in Cancer

MNT – Medical Nutrition Therapy

NCA - Non-competitive antagonist

NF-κB - Nuclear factor kappa-B

NHMRC – National Health and Medical Research Centre

NK1 - Neurokinin 1

PG-SGA – Patient Generated Subjective Global Assessment

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL – Quality of Life

RCT – Randomized Controlled Trial

RP-HPLC – Reverse Phase - High Performance Liquid Chromatography

TxB2 - Thromboxane B2
“[The nausea] was just so consuming at times that I really couldn’t think about anything else, and I just certainly couldn’t, I just couldn’t function. The only thing I could do was just curl up in bed.” - One patient’s description of their experience with chemotherapy-induced nausea and vomiting.