THE EVALUATION AND RISK ASSESSMENT OF COMPLEMENTARY MEDICINE USE BY CANCER PATIENTS TREATED AT AN ACADEMIC HOSPITAL IN JOHANNESBURG

Izel van Heerden

A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science

Johannesburg, 2024.

DECLARATION

I, Izel van Heerden, student number 1949701, declare that this Dissertation is my own, unaided work. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

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(Signature of candidate)

15th day of October 2024 in Fairland

DEDICATION

I dedicate this research to my family and friends. Your patience, understanding and motivation were endless. Thank you for helping me reach this dream.

PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT

The manuscript detailing the results of this research is currently underway and will be submitted for publication. The title of the manuscript will be Complementary medicine use by cancer patients treated at an academic hospital in Johannesburg.

ABSTRACT

Introduction: Globally, the use of complementary and alternative medicines (CAMs) is prevalent among cancer patients and well documented. However, limited data exist on the prevalence and patterns of CAM use amongst cancer patients in South Africa. Since most CAMs are not subjected to the normal quality controls and rigorous clinical trials like registered medications they carry a risk for drug interactions and potential adverse effects. Patients use CAM in the belief that they may offer a cure or to alleviate cancer drug adverse effects. This study aimed to investigate the prevalence and types of CAM used by cancer patients receiving treatment at an academic hospital in Johannesburg, and to identify potential drug-CAM interactions.

Research design and methods: A cross-sectional, descriptive design was employed, with a convenience sample of 120 participants. Part One of the study comprised of data collection using a researcher-administered questionnaire. Part Two of the research entailed a traditional literature review to identify potential drug-CAM interactions and risks associated with the CAMs identified in part one of the study.

Results: CAM usage was reported by a third of respondents (33%; n=40), while the majority (66.7%; n=80) did not utilise CAMs. Among the CAM users, 16 individuals reported using multiple CAMs, resulting in 79 CAMs being reported by 33.3% (n=40) of the respondents. Notably, 21.66% of non-CAM users (n=80) had previously considered using one or multiple CAMs. The data analysis revealed a statistically significant association between CAM use and specific cancer diagnoses. Specifically, respondents with breast cancer ($p = 0.027$) and haematological cancers ($p = 0.039$) demonstrated a significantly higher likelihood of using CAMs compared to patients with other cancer diagnoses. Commonly reported CAMs include biologically based practises including fruits, vegetables, vitamins, minerals, dietary supplements, herbs or medicinal plants. The literature review on the selected products revealed the following: (i) product claims are not substantiated by clinical evidence, (ii) pre-clinical and clinical evidence is insufficient

and not standardised, (iii) claims are not supported by clinical trials (iv) in robust clinical trials the potential for drug-CAM interactions were not considered.

Recommendations: Healthcare professionals should inquire about CAM use among cancer patients. Decision aids may be utilised to support informed decision-making and further research is needed to investigate the safety and efficacy of the identified CAMs to ensure safe use among cancer patients in South Africa.

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LIST OF ABBREVIATIONS

ADR: Adverse Drug Reaction
BAX: B-cell Lymphoma-2-Associated X
BRCA1: BReast CAncer Gene 1
BRCA2: BReast CAncer Gene 2
CAM: Complementary and Alternative Medicine
CBD: Cannabidiol
CI: Confidence Interval
CRC: Colorectal Cancer
CTLA-4: Cytotoxic T-lymphocyte Antigen
CYP: Cytochrome P450 System
DNA: Deoxyribonucleic acid
EGFR: Epidermal Growth Factor Receptor
ER: Oestrogen Receptor
FDA: Food and Drug Administration
HER: Human Epidermal Growth Factor
HR: Hazard Ratio
ICI: Immune Checkpoint Inhibitor
IV: Intravenous
M: Distant Metastasis
mAbs: Monoclonal Antibodies
mCRC: Metastatic Colorectal Cancer
N: Lymph Node Metastasis
PD-1: Programmed Cell Death-1
PDGFR: Platelet-Derived Growth Factor
PR: Progesterone Receptor
ROS: Reactive Oxygen Species
S Phase: DNA Synthesis Phase
SERM: selective oestrogen receptor modulator
T: Primary Tumour Size

THC: Tetrahydrocannabinol

TKIs: Tyrosine Kinase Inhibitors

ALTERNATIVE TERMINOLOGY

Ascorbic acid: Vitamin C

LIST OF SYMBOLS

Cmax: Peak Plasma Concentration

G: Gram

G/Kg: Grams per Kilogram

IC50: Half-maximal Inhibitory Concentration

mg: Milligram

ml: Milliliter

n: Sample Size

nmol: Nanomoles

µg: Microgram

Tmax: Time to Reach Maximal Plasma Concentration

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1 CHAPTER ONE
LITERATURE REVIEW

1.1 Burden of disease

Global cancer epidemiology data presented by The International Agency for Research on Cancer projected approximately 20 million new cancer cases worldwide in 2022, resulting in 9.7 million cancer-related deaths (Ferlay *et al.,* 2022). Statistics indicate that one in five individuals will develop cancer during their lifetime, with a 20% likelihood of cancer onset before the age of 75. The most prevalent cancers globally in 2022 were lung cancer (12.4%), breast cancer (11.6%), colorectal cancer (CRC) (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%). Future projections for 2050 anticipate a significant rise in global cancer diagnoses, exceeding 35 million cases, marking a 77% increase from 2022 figures. This surge in cancer incidence is primarily attributed to an ageing population and heightened exposure to risk factors (Ferlay *et al.,* 2022).

In 2022, South Africa reported 111,321 new cancer cases and 64,547 cancer-related deaths. The most prevalent cancers in the country include breast, prostate, and cervical cancer, with lung cancer exhibiting the highest mortality rates locally (Ferlay *et al.,* 2022). The Department of Health in South Africa has implemented a national strategic framework to address cancer, focusing on prevention, treatment, and the well-being of individuals affected by the disease. This framework prioritises common local cancers and introduces screening programmes for early detection, childhood vaccinations, and disease-specific national cancer care guidelines (Cairncross *et al.,* 2021; Department of Health South Africa, n.d.).

1.2 Causes of cancer

Cell division in normal cells is intricately regulated by a balance of stimulatory and inhibitory signals (Kifle *et al.,* 2021). When exposed to various stressors such as physical, chemical, biological factors, or genetic alterations, disruptions in the normal cell division process can occur. This disruption can lead to accelerated cell proliferation, uncontrolled growth, invasion, and metastasis. Risk factors such as tobacco, aflatoxins, ultraviolet radiation, radon exposure, sedentary lifestyle, and high-calorie diets have been associated with these disturbances (Kifle *et al.*, 2021). Additionally, infection-related

cancers have been linked to pathogens like human papillomavirus, hepatitis B virus, hepatitis C virus, and *Helicobacter pylori* (De Martel *et al.,* 2018). Hormone replacement therapy, comprising oestrogen and progestin, used for managing menopausal symptoms, has been correlated with an increased incidence of postmenopausal breast cancer (Rosenberg *et al.,* 2016). Furthermore, inherited mutations in cancer susceptibility genes *BRCA1* and *BRCA2* significantly elevate the lifetime risk of ovarian or breast cancer in females. These genes play crucial roles in DNA (deoxyribonucleic acid) repair and cell cycle checkpoint activation, and their alteration can lead to chromosomal instability and impaired checkpoint control, fostering tumour development (Clusan *et al.,* 2023). Recent global data from 2019 identified smoking, excessive alcohol consumption and obesity as the primary risk factors contributing to cancer-related deaths in both males and females (Cancer Risk Factors Collaborators, 2019; GBD, 2022).

1.3 Cancer staging and grading

Cancer staging and grading play a crucial role in determining prognosis and guiding treatment decisions in oncology (Greene & Sobin, 2008; Telloni, 2017). The internationally recognised TNM (tumour-node-metastasis) classification system defines cancer's anatomical extent by assessing tumour size (T) and growth, lymph node involvement (N), and distant metastases (M). Once the cancer's clinical stage is determined, treatment strategies are tailored based on physical exams, lab results, and imaging. Biopsy samples are evaluated histologically post-biopsy or surgery to confirm staging (Greene & Sobin, 2008; Telloni, 2017).

Table 1.1 Tumour-node-metastasis classification

Primary tumour size (T)	TX: Primary tumour cannot be assessed T0: No evidence of primary tumour T1, T2, T3, T4: Tumour size and/or extent of the primary tumour.
Lymph node metastasis (N)	NX: Regional lymph nodes cannot be assessed N0: No nodal metastasis N1, N2, N3: Nodal and regional involvement
Distant metastasis (M)	MX: Metastasis cannot be assessed M0: No evidence of metastasis M1: Distant metastasis present

Source: Adapted from (Rosen & Sapra, 2023)

The TNM combinations are also grouped into five simplified stages, as per the outline provided in Table 1.2.

Table 1.2 Cancer stage grouping

Staging	Description
Stage 0	Indicates carcinoma in situ. Tis, N0, M0.
Stage I	Localized cancer. T1-T2, N0, M0.
Stage II	Locally advanced cancer, early T1-T2, N1, M0.
Stage III	Locally advanced cancer, late stages. T1-T4, N2-N3, M0.
Stage IV	Metastatic cancer. T1-T4, N1-N3, M1.

Source: (Rosen & Sapra, 2023, para.13)

Cancer grading involves assessing the microscopic appearance of tumour cells and tissues. Low-grade tumours exhibit normal-looking cells and well-differentiated structures, while high-grade tumours show abnormal cells and poorly differentiated structures, indicating aggressiveness and a poorer prognosis (Rosen & Sapra, 2023). Molecular testing and biomarker analysis are now standard practices to identify treatment options, such as anti-hormonal therapy or monoclonal antibodies (mAbs) in breast cancer, based on tumour susceptibility. Gene expression profiling also helps predict disease outcomes and guide adjuvant chemotherapy decisions (Wellstein, 2023)

1.4 Hallmarks of cancer

Cancer is a complex disease characterised by the transformation of normal cells into aberrant cells that exhibit uncontrolled proliferation and altered cellular processes (Hanahan & Weinberg, 2011). These modifications can affect critical cellular mechanisms, including DNA repair, cell cycle regulation, cellular senescence, and apoptosis. Cancer cells acquire a range of capabilities that enable them to proliferate indefinitely, resist growth-inhibitory signals, induce angiogenesis, invade adjacent tissues, and metastasise to distant organs. They become autonomous in their growth, insensitive to negative growth regulatory signals, and develop adaptive mechanisms to

evade immune surveillance and therapeutic interventions. Additionally, tumour development is influenced by extrinsic factors, including tissue inflammation and the host's immune response (Hanahan & Weinberg, 2011).

1.4.1 An overview of the cell cycle and deregulation during cancer

The cell cycle is an intricately regulated process comprising multiple distinct phases, with progression from one phase to the next meticulously controlled by a series of events and checkpoints to ensure the accurate duplication and division of the cell (Dang & Wei, 2021). The cell cycle encompasses the sequence of events that culminate in cell division and duplication, including the non-divisive interphase and the mitotic (M) phase, during which cell division occurs. Interphase is further subdivided into three distinct phases: G1 (the first gap phase), S (the DNA synthesis phase), and G2 (the second gap phase) (Alberts *et al.*, 2002).

The G1 phase is characterised by cellular growth, protein synthesis, and preparation for DNA replication, with multiple signalling pathways and checkpoints ensuring the cell's readiness to proceed to the next phase. The S phase is marked by DNA replication, a critical process that maintains genomic integrity and fidelity by ensuring identical copies of genetic material for daughter cells. Following replication, the cell enters G2, where it continues to grow, replenish energy, and synthesise proteins essential for chromosome manipulation. Organelle duplication and cytoskeletal disassembly occur, providing resources for the mitotic spindle. The cell also checks for DNA damage and ensures proper replication before entering the mitotic phase (M phase) (Alberts *et al.,* 2002).

The M phase encompasses cell division, where replicated chromosomes are segregated into two daughter cells through a multistep process. Mitosis, the first portion of the M phase, consists of five stages (prophase, metaphase, anaphase, telophase, and cytokinesis) that accomplish nuclear division. Cytokinesis, the second portion, affects the physical separation of cytoplasmic components into two daughter cells. Each sub-phase of mitosis is characterised by specific events that ensure accurate chromosome distribution (Alberts *et al.,* 2002).

Deregulation of the cell cycle, characterised by the loss of critical checkpoints, is a hallmark of cancer development (Engeland, 2022). The disruption of cell cycle control leads to uncontrolled proliferation, a fundamental characteristic of cancer (Ding *et al.,* 2020; Rubin *et al.,* 2020). Many chemotherapeutic agents exert their effects by inducing DNA damage, with maximum efficacy during the S phase of the cell cycle when DNA synthesis occurs. Additionally, some treatments target cells entering mitosis, exploiting the vulnerability of the mitotic spindle during this phase (M phase). This highlights the importance of understanding cell cycle regulation and its dysregulation in cancer, enabling the development of targeted therapeutic strategies (Wellstein, 2023).

1.5 Treatment of cancer

The treatment of cancer is a complex process that depends on various factors, including the type of cancer, tumour burden, pathology scores, patient profile, and comorbidities (Subramani & Lakshmanaswamy, 2017). The treatment options encompass surgical resection, radiation therapy, and systemic therapy, which comprises multiple classes of drugs, including traditional chemotherapy, protein-kinase inhibitors (tyrosine kinase inhibitors (TKIs)), pathway-targeted small molecules, antibodies, chimeric antigen receptor T-cells, proteins, and hormone therapy or related agents (Wellstein, 2023). The primary objective of chemotherapy is to achieve complete eradication of cancer cells (Anand *et al.,* 2023). The American Society of Clinical Oncology has established guidelines for the administration of chemotherapy, hormone, or targeted treatments in the neoadjuvant setting for breast cancer based on tumour characteristics such as histology, grade, stage, and biomarker status (Rubens *et al.,* 1965). Neoadjuvant therapy is used as first-line therapy prior to surgical intervention, particularly in breast conservation, to reduce tumour size and simplify surgical resection (Tamirisa & Hunt, 2022). In contrast, adjuvant systemic therapy is initiated post-operatively to eradicate micrometastatic disease, reduce the risk of distant recurrence, and prolong overall survival (Fisher *et al.,* 1997).

1.5.1 Drugs used to treat cancer

The advancement of cancer therapeutics is a direct consequence of our enhanced understanding of cancer biology and the deciphering of the cancer genome (Wellstein,

2023). The identification of cancer-specific targets, including growth factor receptors, dysregulated intracellular signalling pathways, epigenetic modifications (changes in gene expression without changing the DNA sequence), tumour angiogenesis, DNA repair defects, apoptosis pathways, and immune evasion mechanisms, has led to the development of targeted therapies. A notable breakthrough is the emergence of chimeric antigen receptor T-cell treatments (Wellstein, 2023). Currently, four primary classes of chemotherapeutic agents are employed clinically for systemic cancer treatment: traditional cytotoxic agents, hormone therapies, targeted therapies, and immune checkpoint inhibitors (ICIs) (Shuel, 2022). While most of these drugs are administered intravenously, the development of targeted therapies has led to an increase in orally available agents (Wellstein, 2023).

1.5.1.1 Chemotherapeutic agents

Chemotherapeutic agents are classified, and their mechanism of action is understood based on the specific stage of the cell cycle they target. Vinca alkaloids, for instance, exhibit their cytotoxic effects by damaging DNA and disrupting cell reproduction across various cell cycle phases (Mollaei *et al.,* 2021). Topoisomerase I and II inhibitors, on the other hand, exert their effects by impeding topoisomerase activity, thereby preventing DNA replication. Additionally, certain chemotherapeutic agents modulate the quality of cellular proteins and interfere with essential cellular physiological pathways (Anand *et al.,* 2023). A comprehensive overview of these chemotherapeutic agents is presented in Table 1.3, highlighting their diverse mechanisms of action and cellular targets.

Table 1.3 A summary of traditional chemotherapeutic agents

Class of Drugs	Group	Examples	Main Mechanism of Action
Alkylating and related agents	Nitrogen mustards	Cyclophosphamide, ifosfamide, chlorambucil, melphalan, estramustine	Intrastrand cross-linking of DNA
	Nitrosoureas	Lomustine, carmustine	
	Platinum compounds	Carboplatin, cisplatin, oxaliplatin	
	Other	Busulfan, treosulfan, thiotepa, dacarbazine, procarbazine, temozolomide	
Antimetabolites	Folate antagonists	Methotrexate, raltitrexed, pemetrexed	Obstruct DNA and /or RNA synthesis
	Pyrimidineanalogues	Fluorouracil, capecitabine, cytarabine, gemcitabine, tegafur	
	Purine analogues	Fludarabine, cladribine, mercaptopurine, tioguanine, pentostatin, clofarabine, nelarabine	
Cytotoxic antibiotics	Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin, (mitoxantrine), (amascrine)	Multiple effects on DNA/ RNA synthesis and topoisomerase action
	Other	Bleomycin, dactinomycin, mitomycin	

Class of Drugs	Group	Examples	Main Mechanism of Action
Plant derivatives	Taxanes	Paclitaxel, docetaxel	Microtubule assembly prevents spindle formation inhibition of topoisomerase
	Vinca alkaloids	Vinblastine, vincristine, vindesine, vinorelbine,	
	Campothecins	Irinotecan, topotecan, trabectedin	
	Other	Etoposide	

Source: Adapted from (Kifle *et al.,* 2021)

1.5.1.2 Hormone antagonists and inhibitors or hormone analogues

Certain neoplasms exhibit a high degree of hormone dependence or regulation (Clusan *et al.,* 2023). Endocrine therapy plays a crucial role in inhibiting tumour growth in hormone receptor-positive cancers. These therapies disrupt or downregulate the expression of genes and gene networks involved in tumour growth and survival. Research has extensively investigated hormone receptor-positive breast, prostate-, and endometrial cancer treatments. Approved therapies exhibit diverse mechanisms of action, including oestrogen and androgen antagonists, hormone synthesis inhibitors, and gonadotropin-releasing hormone analogues or antagonists (Isaacs *et al*., 2023).

Healthy breast tissue comprises luminal and basal cells, with luminal cells expressing hormone receptors such as oestrogen (ER), progesterone (PR) and prolactin. The expression of ER and/or PR in breast cancer increases the likelihood of endocrine responsiveness (Clusan *et al*., 2023). Tamoxifen, a competitive partial agonist inhibitor of oestradiol at the ER, is classified as a selective oestrogen receptor modulator (SERM). Inhibition of androgen and ER activation or activity hinders the expression of genes and gene networks, promoting tumour growth and survival. SERMs are employed as palliative treatment or chemoprevention in postmenopausal women at high risk of developing breast cancer. Anastrozole and letrozole, selective nonsteroidal aromatase inhibitors, reduce oestrogen production, demonstrating efficacy in tumours resistant to SERMs and selective ER down regulators used in women with metastatic breast cancer progressing on anti-oestrogen therapy (Isaacs *et al.,* 2023).

Goserelin, a synthetic decapeptide analogue of luteinising hormone-releasing hormone (LHRH), is clinically approved for the treatment of advanced prostate and breast cancers amenable to hormonal manipulation. LHRH is a hypothalamic hormone that regulates the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Prolonged administration of goserelin leads to the suppression of pituitary LH secretion, resulting in decreased serum testosterone levels in males and oestradiol concentrations in females (AstraZeneca, 2022). Additionally, androgen inhibitors have been approved for various applications, including monotherapy or adjuvant treatment in combination with radical prostatectomy or radiotherapy for locally advanced, non-metastatic prostate cancer where surgical or medical castration is not appropriate (AstraZeneca, 2017). A comprehensive summary of hormone antagonists, inhibitors, and analogues used in cancer treatment is presented in Table 1.4.

Table 1.4 Summary of hormone antagonists, inhibitors or hormone analogues used to treat cancer

Class of Drugs	**Drugs**
Selective oestrogen receptor modulators	Tamoxifen, toremifene
Selective oestrogen receptor degraders	Fulvestrant
Aromatase inhibitors	Anastrozole, letrozole, exemestane
Gonadotropin-releasing hormone(GnRH) analogues: (i)GnRH agonists (ii)GnRH antagonists	Goserelin, leuprolide, buserelin, histrelin, triptorelin Degarelix, cetrorelix, relugolix
Non-steroidal androgen receptor antagonist	Bicalutamide, enzalutamide, apalutamide, darolutamide
Progesterone receptor agonists	Megestrol acetate, medroxyprogesterone acetate
Inhibitors of Steroidogenesis	Abiraterone

Source: Adapted from (Isaacs *et al.,* 2023)

1.5.1.3 Targeted therapies

Targeted therapies are precisely designed small molecules or mAbs that disrupt tumour growth by inhibiting oncogenic pathways crucial for cancer cell proliferation and survival (Shuel, 2022). These targeted agents act on specific cell surface antigens, growth factors, receptors, or signal transduction pathways that drive key cellular processes, including cell cycle progression, proliferation, metastasis, and angiogenesis. Currently, targeted treatments are categorised into two distinct classes: small molecule inhibitors and larger molecules, such as mAbs. This classification reflects their unique mechanisms of action and structural properties, enabling tailored approaches to cancer treatment (Shuel, 2022).

1.5.1.3.1 Small molecule inhibitors

Small molecule inhibitors are organic compounds with a molecular weight of less than 1000 Daltons, enabling them to penetrate cells and exert their intracellular effects (Wellstein & Giaccone, 2023). These molecules often exhibit a broader spectrum of activity, as they can inhibit multiple targets and are typically administered orally. TKIs are a prominent class of small molecule inhibitors that bind to the intracellular kinase domain and inhibit the enzymatic activity of epidermal growth factor receptor (EGFR). EGFR mutations lead to constitutive activation of the kinase, driving cancer cell growth and survival (Wellstein & Giaccone, 2023). Specific examples of TKIs include erlotinib, gefitinib, afatinib, osimertinib and dacomitinib, which have been developed to target EGFR mutations. A list of small molecule inhibitors and their corresponding targets is presented in Table 1.5.

Table 1.5 List of small molecule inhibitors

Small Molecule Inhibitors	**Drugs**
Growth Factors and Receptors Inhibitors	
Epidermal growth factor receptor inhibitors	Erlotinib, gefitinib, afatinib, osimertinib, dacomitinib
Epidermal growth factor /human epidermal growth factor inhibitors	Lapatinib, neratinib, tucatinib
Inhibitors of Intracellular Protein Kinase	
Mutant B-RAF kinase inhibitors	Vemurafenib, dabrafenib
Mitogen-activated protein kinase inhibitors	Cobimetinib, trametinib
Janus-associated protein kinase inhibitors	Ruxolitinib
Cyclin-dependant kinase 4/6 inhibitors	Palbociclib, abemaciclib, ribociclib
Bruton tyrosine kinase inhibitors	Ibrutinib
BCR-ABL, platelet-derived growth factor receptor , KIT kinase inhibitors	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib
Anaplastic lymphoma kinase inhibitors	Crizotinib, alectinib, ceritinib
Phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitors	Idelalisib
Mechanistic or mammalian target of rapamycin inhibitors	Temsirolimus, everolimus
Multikinase inhibitors	Cabozantinib, vandetanib
Inhibitors of Tumour Angiogenesis	
Inhibitor of hypoxia-inducible factor activity	Belzutifan
Inhibitor of vascular endothelial growth factor and intracellular kinases participating in angiogenesis	Sunitinib, sorafenib, axitinib, lenvatinib, pazopanib, regorafenib
Poly(ADP-Ribose) Polymerase Inhibitors	
Poly(ADP-Ribose) Polymerase inhibitor	Olaparib
Modulators of Protein Degradation	
Thalidomide and congeners	Thalidomide, lenalidomide, pomalidomide
Proteasome inhibitors	Bortezomib

Small Molecule Inhibitors	Drugs
Epigenetic Modulators	
Epigenetic modulator	Panobinostat
Other inhibitors	
B-cell lymphoma-2 (antiapoptotic protein)	Venetoclax

Source: Adapted from (Wellstein & Giaccone, 2023)

1.5.1.3.2 Monoclonal antibodies

mAbs are large protein molecules comprised of amino acids (Micheel, 2006). Their size precludes them from entering cells, and instead, they bind to receptors or proteins on the surface of cancer cells or in the tumour microenvironment (Shuel, 2022). mAbs exert their anti-tumour effects through various mechanisms, including inhibition of growth receptors, serving as drug-conjugate carriers, recruiting immune cells, and forming antigen-antibody complexes (Micheel, 2006). The human epidermal growth factor receptor 2 (HER2) is a proto-oncogene and member of the HER family, whose overexpression drives intracellular tyrosine kinase and oncogenic signalling, even in the absence of activating mutations, co-receptors, or ligands (Ahn *et al.,* 2020). HER2 positivity is observed in 20% of human breast cancers, correlating with a higher risk of disease recurrence. Trastuzumab, a humanised monoclonal antibody targeting HER2, binds to the extracellular domain, preventing receptor dimerisation and downstream signalling activation (Greenblatt & Khaddour, 2022). Table 1.6 provides a comprehensive overview of monoclonal antibody classes and their corresponding targets.

Table 1.6 Monoclonal antibodies and their targets

Class of Monoclonal Antibodies	Drugs
EGFR inhibitors	Cetuximab, panitumumab, necitumumab
EGFR/HER2 inhibitors	Trastuzumab, pertuzumab
PDGFR Inhibitors	Olaratumab
VEGFR Inhibitors	Bevacizumab, ramucirumab
Antibodies Targeting Cell Surface Antigens	Rituximab, ofatumumab, obinutuzumab, alemtuzumab dinutuximab, daratumumab, elotuzumab, blinatumomab

Source: Adapted from (Wellstein & Atkins 2023)
EGFR: epidermal growth factor; HER2: human epidermal growth factor receptor 2; PDGFR: platelet-derived growth factor; VEGFR: vascular endothelial growth factor receptor

1.5.1.3.3 Immune checkpoint inhibitors

Immune checkpoint inhibitors modulate the immune response to cancer by targeting negative regulators of immune activation, such as cytotoxic T-lymphocyte antigen (CTLA-4) and programmed cell death-1 (PD-1) (Wellstein & Atkins, 2023). Normally, these checkpoints prevent excessive immune activation and autoimmunity. However, cancer cells exploit them to evade immune surveillance. ICIs, including anti-cytotoxic T-lymphocyte-associated protein-4 (ipilimumab) and anti-programmed cell death protein-1 (nivolumab, pembrolizumab), work by (i) blocking CTLA-4, enhancing T-cell activation and proliferation, (ii) inhibiting PD-1, allowing T cells to recognise and attacking cancer cells more effectively. This leads to enhanced antigen presentation, increased T-cell infiltration into tumours, and improved antitumor immune responses. ICIs have transformed cancer treatment, offering improved outcomes and new possibilities for combination therapies (Wellstein & Atkins, 2023). Examples of immunotherapeutic agents include antibodies targeting immune inhibitory receptors, such as CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab) and programmed cell death ligand-1 (atezolizumab) (Shiravand *et al.*, 2022).

1.5.2 Adverse reactions associated with cancer drugs

Chemotherapeutic agents exert their cytotoxic effects by targeting cell division, a process that is exploited by rapidly proliferating cancer cells, as well as certain normal tissues (Anand *et al.,* 2023). However, the non-selective nature of these agents leads to concomitant damage to normal host cells in the bone marrow, hair follicles and intestinal epithelium, resulting in adverse drug reactions (ADRs). Specific classes of drugs are often associated with distinct adverse effects, such as alkylating agents, which are linked to myelosuppression and gastrointestinal disturbances (e.g., nausea, vomiting, diarrhoea, and anorexia). Spindle poisons and platinum drugs are known to cause peripheral neuropathy, while anthracyclines can induce myelosuppression and both acute and chronic cardiotoxicity (Anand *et al.,* 2023). Notably, most chemotherapeutic drugs possess a narrow therapeutic index (Chang *et al.,* 2021), necessitating precise dosing to achieve efficacy without incurring unacceptable toxicity. Minor deviations in dosage can result in inefficacy or toxicity (Habet, 2021).

An ADR is defined as a harmful and unintended response to a medication, as stated in the Guideline for Adverse Drug Reactions by the South African Health Products Regulatory Authority (SAHPRA, 2020). ADRs can arise from a drug's lack of efficacy, unexpected responses at approved dosages or increased doses, or misuse/abuse of the medication. These reactions may be previously recognised or unknown. Adverse events are systematically graded based on their severity, with the Common Terminology Criteria for Adverse Events classifying them as Grades 1-5, according to clinical descriptions of severity (National Cancer Institute, 2017). A comprehensive overview of the grading system is presented in Table 1.7.

Table 1.7 Grading of adverse events described by the National Cancer Institute

Grading	Clinical Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not required
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening; urgent intervention required
Grade 5	Death associated with the adverse event

Source: (National Cancer Institute, 2017, p2)

A prospective observational study conducted by Krishnarajan *et al.* (2021) investigated the incidence and impact of chemotherapy-induced ADRs on the quality of life in cancer patients at a tertiary care hospital in Tamil, India. The study observed 228 ADRs in 73 patients, with nausea and vomiting being the most prevalent (45%, n=34), followed by fatigue (41%, n=31), alopecia (33%, n=25), and anaemia (27%, n=20). The affected organ systems included the gastrointestinal tract (36.4%), musculoskeletal system (22.4%), dermal system (17.1%), myelosuppression (9.6%), and nervous system (7.5%), highlighting the diverse range of chemotherapy-induced toxicities. These findings underscore the need for enhanced monitoring and management of ADRs to improve cancer care outcomes.

Chemotherapeutic agents are associated with a wide range of ADRs (Anand *et al.*, 2023). Targeted drugs offer a significant advantage in minimising off-target toxicities on adjacent tissues and organs. However, targeted drugs are not without adverse effects, and combination therapy with chemotherapeutic agents may exacerbate treatment-related toxicities (Anand *et al.,* 2023). For instance, checkpoint inhibitors can trigger inflammatory toxicities in organs, leading to immune-related adverse events (Dougan *et al.*, 2021). Table 1.8 provides examples of specific targeted agents and their commonly reported drug-related adverse effects. Due to the plethora of adverse reactions associated with

cancer therapy, patients may seek alternative treatments outside of conventional medical care to manage their symptoms (Drozdoff *et al.,* 2019).

Table 1.8 Examples of targeted therapies and commonly reported drug-related adverse effects

Anticancer Therapy	**Drug**	**Therapeutic Use**	**Common Adverse Effects**
Targeted Therapy			
mAbs			
EGFR/HER2 inhibitor (Wellstein & Atkins, 2023)	Trastuzumab	HER-2 overexpressed breast- and gastric cancer in combination with cytotoxic agents or monotherapy	Acute adverse effects include: infusion-related fever, chills, nausea, dyspnea and rashes. Serious is cardiotoxicity
VEGFR Inhibitors (Wellstein & Atkins, 2023)	Bevacizumab	Indicated for the treatment of various cancers: metastatic colon cancer, non-small cell lung cancer (NSCLC), ovarian-, cervical, renal cell carcinoma (RCC) as well as glioblastoma. Used as monotherapy or in combination.	Serious class-related adverse effects: hypertension, gastrointestinal perforation, thromboembolic events and haemorrhage, as well as epistaxis

Anticancer Therapy	Drug	Therapeutic Use	Common Adverse Effects
ICIs			
PD-1 inhibitor (Wellstein & Atkins, 2023)	Nivolumab	Indicated as monotherapy or combination therapy in multiple cancers: advanced or resected high-risk melanoma, previously treated advanced NSCLC, RCC, advanced head and neck cancer, MSI-H or mismatch repair-deficient colorectal cancer, hepatocellular carcinoma and relapsed/refractory classical Hodgkin lymphoma	Adverse effects in therapy of melanoma include rash; advanced squamous NSCLC, adverse effects: fatigue, dyspnea, pneumonitis, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. Immune-mediated adverse effects: pneumonitis, colitis, hepatitis, nephritis, and renal dysfunction
Inhibitors of Intracellular Protein Kinases			
BCR-ABL, platelet-derived growth factor receptor (PDGFR), KIT kinase inhibitors (Wellstein & Giaccone, 2023)	Imatinib	Chronic myeloid lymphoma, also effective in other tumours, including GISTs (driven by a c-KIT mutation), hypereosinophilic syndrome, and dermatofibrosarcoma protuberans	Cause gastrointestinal symptoms (diarrhoea, nausea and vomiting); promotes fluid retention; can cause myelosuppression, hepatotoxicity
Other			
BCL2 (antiapoptotic protein) (Wellstein & Giaccone, 2023)	Venetoclax	Chronic lymphocytic leukaemia or small lymphocytic lymphoma.	Adverse effects: neutropenia, gastrointestinal, anaemia, upper respiratory tract infection, thrombocytopenia and fatigue; may cause foetal harm

Source: Various as indicated
BCL2: B-cell lymphoma-2; EGFR: epidermal growth factor; GIST: gastrointestinal stromal tumour; HER2: human epidermal growth factor receptor 2; ICIs: Immune checkpoint inhibitors; mAbs: monoclonal antibodies; PD-1 Programmed cell death-1; PDGFR: platelet-derived growth factor; VEGFR: vascular endothelial growth factor receptor

1.5.3 Resistance to cancer drugs

Multi-drug resistance (MDR) can occur intrinsically or be acquired during treatment initiation (Wang *et al.,* 2019; Mollaei *et al.*, 2021). The primary mechanisms driving multi-drug resistance include the activation of additional driver proto-oncogenes, mutations or

altered expression levels of drug targets, and changes in the tumour microenvironment (Wang *et al.,* 2019). The underlying resistance mechanisms involve cancer cell drug efflux, overexpression of anti-apoptotic proteins, enhanced drug metabolism, increased expression or mutations of drug targets, and augmented DNA repair mechanisms (Pan *et al.,* 2016; Wang *et al.*, 2023). To circumvent drug resistance to chemotherapeutic agents, targeted therapy is incorporated into cancer treatment, leveraging a synergistic effect to normalise blood flow, enhance apoptosis and inhibit pro-survival signals from growth factor pathways (Wellstein, 2023).

1.6 Complementary and Alternative Medicine

Complementary and Alternative Medicine (CAM) encompasses a diverse range of medical practices and products that fall outside the scope of evidence-based modern Western medicine. Despite the lack of scientific evidence, aggressive marketing and promises of miracle cures often entice patients to use CAM alongside conventional medicine (Zwartz, 2021). CAM therapies can be used in conjunction with conventional medical approaches (Subramani & Lakshmanaswamy, 2017) or as an alternative treatment to allopathic medicine (National Center for Complementary and Integrative Health, n.d. a). Integrative medicine combines conventional medical and CAM approaches in multimodal therapy (Zwartz, 2021). CAM is categorised into five main groups: (i) Mind-body therapies (e.g., meditation, yoga, tai chi), (ii) Biologically based practices (e.g., vitamins, minerals, dietary supplements, herbs), (iii) Manipulative and body-based practices (e.g., massage therapy, chiropractic care, reflexology), (iv) Energy healing (e.g., Reiki, therapeutic touch), and (v) Whole medical systems (e.g., ayurvedic medicine, traditional Chinese medicine, naturopathic medicine). These systems often have cultural and historical roots and may incorporate various techniques such as diet, herbal medicines, exercise, meditation, and acupuncture to restore balance and promote health (National Cancer Institute, n.d.). The National Centre for Complementary and Integrative Health has updated these categories of CAM practices based on their primary therapeutic input or delivery method, resulting in five distinct categories: (i) Nutritional practices (formerly classified as biologically-based practices), (ii) Psychological practices, (iii) Physical practices (previously referred to as body-mind practices), (iv) Combinations of practices (integrating nutritional, physical and psychological approaches), and (v) Other

practices, including traditional Chinese medicine, ayurvedic medicine and other modalities (National Center for Complementary and Integrative Health, n.d. a). This categorisation system provides a framework for understanding the diverse range of CAM therapies and their underlying mechanisms, as well as an overlap of these health practices.

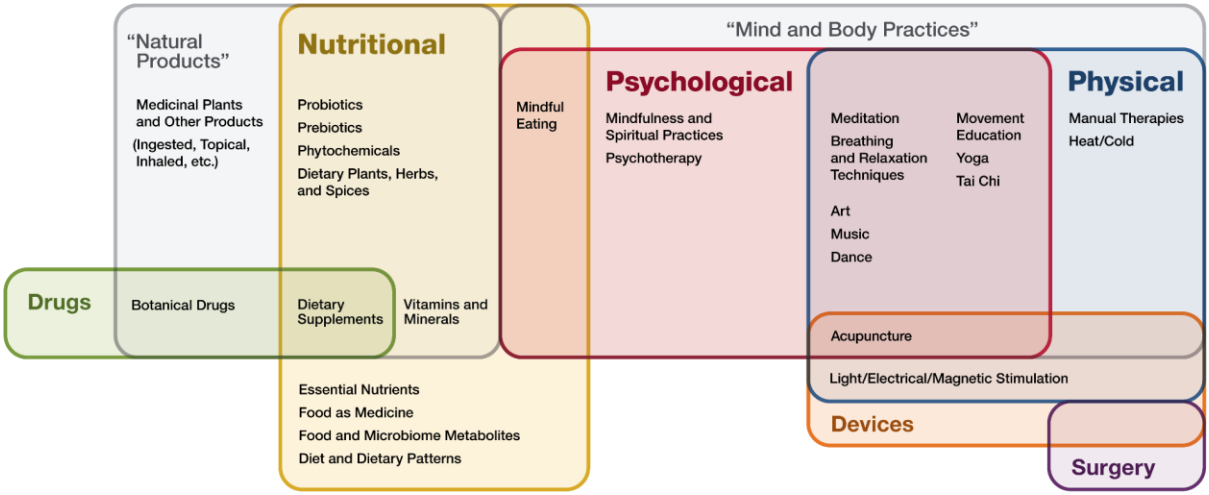

Figure 1.1 Examples of complementary health practices that fall within the categories of psychological, physical and nutritional

Source: (National Center for Complementary and Integrative Health, n.d. a, no pagination)

CAM is not held to the same rigorous standards of scrutiny and investigation as conventional medications approved by regulatory authorities such as the Food and Drug Administration (FDA) or the European Medicine Agency (Baars *et al.,* 2019; Knecht *et al.,* 2020). To address this knowledge gap, the National Centre for Complementary and Integrative Health was established to evaluate the scientific evidence supporting the efficacy and safety of CAM practices (National Center for Complementary and Integrative Health, n.d.). Unfortunately, the lack of scientific evidence renders patients vulnerable to misinformation and anecdotal claims, particularly on the Internet (Ventola, 2010; Power & Hopayian, 2011; Fisher *et al.*, 2014). This highlights the need for critical evaluation and evidence-based information to inform healthcare decisions.

1.7 Complementary and Alternative Medicine use by cancer patients

The utilisation of CAM among cancer patients has increased globally in recent years (Molassiotis *et al.,* 2005; Keene *et al.,* 2019; Wolf *et al.*, 2022), reflecting a growing interest in holistic and integrative approaches to healthcare (Escudero-Vilaplana *et al.,* 2023). A meta-analysis, including multi-country surveys conducted in adult cancer patients, revealed a significant rise in CAM use, from approximately 25% in the 1970s and 1980s to over 32% in the 1990s and 49% after 2000 (Horneber *et al.*, 2012). A subsequent systematic review reported global CAM use in 51% of cancer patients (Keene *et al.*, 2019). In Africa, a survey found high rates of CAM use among cancer patients, with 65% in Nigeria and over 70% in Ethiopia and Ghana (James *et al.*, 2018). In South Africa, limited data exists, but a small study conducted in a public hospital in Cape Town in 2022 reported that 12 out of 17 patients interviewed used CAMs, including various herbal remedies (cancer bush tea extract, buchu, *Sutherlandia* tablets, marijuana oil and seeds) ointments (Vicks, Uncle Daan's and Olive wood), cornflour, homoeopathy and alternative therapies (Githaiga & Swartz, 2022).

1.8 Predictive factors of Complementary and Alternative Medicine use

Several predictors have been identified to determine the likelihood of cancer patients using complementary medicine (Guillaud *et al.,* 2019). These predictors can be categorised into demographic, clinical, psychosocial, and healthcare-related variables. In Europe, a systematic review found that being female is a positive predictive factor for using CAM therapy (Guillaud *et al.,* 2019). Similarly, in cancer patients, demographic predictors include gender (female), higher education, younger age, and higher income (Keene *et al.,* 2019). Females are more likely to seek diverse healthcare approaches and discuss their diagnosis with others, while higher education and income may lead to questioning conventional practices and seeking alternative options. Younger patients may seek additional treatments due to a perceived threat to their future plans. In a US-based cancer centre, older females were more likely to use CAM, contradicting the younger age predictive factor (Judson *et al.,* 2017). Biologically based interventions were the most common CAM approach. In Germany, younger age (<62 years) was significantly associated with CAM use (Wolf *et al.,* 2022). In Australian males with cancer, metastatic disease, active religious practice, and tertiary education were independent predictors of

CAM use (Klafke *et al.,* 2012). These findings suggest that demographic factors play a significant role in predicting CAM use among cancer patients.

1.9 The justification behind Complementary and Alternative Medicine use

The increasing popularity of CAM reflects a growing interest among cancer patients in seeking holistic approaches to manage their disease. The primary motivations for CAM use among cancer patients are centred around their needs to (1) find a cure, (2) manage cancer-related symptoms, and (3) alleviate adverse effects associated with chemotherapy (Lyman *et al.*, 2018; Keene *et al.*, 2019; Crichton *et al.,* 2021). A study done in Spain revealed the following primary reasons for CAM use among cancer patients: (i) improvement of general well-being (21.4%), (ii) habitual consumption (21.2%), (iii) management of weight loss or constipation (15.2%), (iv) treatment of drug-induced adverse effects (8.6%), (v) enhancement of the immune system (7.9%), (vi) mental health support (5.9%), (vii) treatment of the cancer (4.8%), (viii) insomnia relief (2.3%), and (ix) cancer prevention and other reasons (12.7%) (Escudero-Vilaplana *et al*., 2023). These findings highlight the diverse reasons behind CAM use among cancer patients, underscoring the need for healthcare professionals to participate in open discussions with patients about their CAM use and preferences.

1.10 Disclosure of Complementary and Alternative Medicine use to the oncologist

Disclosure of CAM use to oncologists is crucial to mitigate potential risks associated with CAM use (Baum *et al.,* 2006). However, a significant proportion of patients (up to 77%) fail to disclose their CAM use to their treating physicians (Davis *et al.*, 2012). The reasons for non-disclosure include the lack of inquiry by healthcare providers, patients' anticipation of disapproval or judgment, and the perception that CAM use is unrelated to conventional care. A systematic review and meta-analysis by Foley *et al*. (2019) reported a similar low disclosure rate of 33% for biologically based complementary medicine, citing additional reasons such as patients' belief in the lack of knowledge about complementary medicine among healthcare providers, limited time with doctors, and the misconception that these products are safe. Language barriers and disregard for cultural values also hinder disclosure of CAM use, as observed among breast cancer patients in South Africa (Githaiga & Swartz, 2022). The non-disclosure of CAM use leads to the underreporting of

potential risks associated with CAM use, highlighting the need for healthcare providers to facilitate open discussions with their patients about CAM use (Awortwe *et al.,* 2018).

1.11 Risks associated with Complementary and Alternative Medicine use

The general public often perceives plant-based remedies or products as "natural" and safe (Ektor, 2014; Van Wyk & Prinsloo, 2020), but the concurrent use of complementary medicine with conventional cancer therapy can pose significant risks to patients (Huebner *et al*., 2013). The pharmacological activities and enzyme interactions of CAMs can lead to decreased efficacy of cancer drugs or increased toxicity risks (Cheng *et al.*, 2023). Several studies have investigated the prevalence of potential CAM-drug interactions with conventional anticancer treatment, reporting high frequencies of possible interactions. For instance, Wolf *et al.* (2022) identified potential CAM-drug interactions in 51.2% of CAM supplement users, while Firkins *et al.* (2018) found a risk of interactions in 54.9% of CAM users on conventional therapy. These findings highlight the importance of scrutinising CAM use in cancer patients to mitigate potential harmful interactions.

1.11.1 Complementary and Alternative Medicine-related adverse effects

Despite the concerns about increased adverse effects associated with biologically-based CAM in cancer treatment, cancer patients continue to utilise integrative therapy (Knecht *et al.,* 2020). The Society for Integrative Oncology (SIO), a multidisciplinary team spanning several countries, aims to investigate the application of evidence-based integrative medicine in cancer treatment. SIO developed clinical practice guidelines for the use of integrative therapies as supportive care in breast cancer patients, emphasising the importance of continuous evaluation of supplement intake to assess potential adverse effects or interactions (Greenlee *et al.,* 2014). Although the risk of adverse reactions increases when combining CAM with conventional therapy, it is challenging to determine whether the adverse effect is attributed to CAM, disease symptoms, or CAM-drug interactions (Knecht *et al.,* 2020). CAM-related adverse effects are commonly associated with allergic reactions or gastrointestinal problems, while occasional serious adverse events, including hepatotoxicity, neurotoxicity, or nephrotoxicity, have been reported in the literature (Jermini *et al.,* 2019).

1.11.2 Complementary and Alternative Medicine-drug interactions

Cancer patients frequently utilise biologically based or nutritional CAM despite the potential risks of interaction with anticancer drugs (Knecht *et al.*, 2020). However, when informed about CAM use, many oncologists in clinical practice encounter difficulties in identifying the mechanism and assessing the severity of possible interactions or risks to patients (Pourroy *et al.,* 2017). These interactions can lead to various consequences, including adverse effects, reduced efficacy of cancer treatment, and enhanced toxicity (Jermini *et al.,* 2019). The lack of clear understanding and communication about CAM use among healthcare providers and patients highlights the need for improved education and guidance on CAM-drug interactions in oncology practice.

1.11.2.1 The effects of antioxidants on the efficacy of chemotherapy

Anticancer treatment generates reactive oxygen species (ROS), which induces programmed cell death (Liou & Storz, 2010). However, antioxidants suppress free radical formation (Yasueda *et al.*, 2016). In cancer cells, elevated ROS production is a result of increased metabolic rate, influencing signalling pathways involved in cell proliferation, apoptosis, and gene mutation (Perillo *et al.,* 2020). Combining antioxidants with anticancer treatment may interfere with ROS production, leading to cell proliferation and progression (Ladas *et al.,* 2004). For instance, doxorubicin, a chemotherapy drug, disrupts DNA repair and generates free radicals, causing lipid peroxidation, membrane and DNA damage, oxidative stress, and cell cycle arrest in both malignant and healthy cells (Thorn *et al.*, 2011). Despite this, antioxidant supplementation is common among cancer patients (Ambrosone *et al.,* 2019). The Long Island Breast Cancer Study Project found that 60.5% used antioxidants during adjuvant treatment, with vitamins C and E, selenium, and β-carotene being the most commonly used (Greenlee *et al.,* 2009). However, a phase-3 trial (S0221) conducted in the USA reported that antioxidant supplementation during breast cancer treatment increased the risk of cancer recurrence by 41%. Additionally, vitamin B12 use before and during chemotherapy was associated with lower disease-free survival and overall survival (Ambrosone *et al.,* 2019).

1.11.2.2 Drug receptors, pharmacokinetics and pharmacodynamics in CAM-drug interactions

Drug receptors are components of a cell or organism responsible for interacting with a drug that initiates a chain of events to produce the drug's observed effects (von Zastrow, 2024). Drug receptors are proteins responsible for mediating the actions of endogenous chemical signals of many therapeutic agents. Other classes of proteins have also been identified as drug receptors (von Zastrow, 2024). Drug binding to enzymes may be inhibited or enhanced. Cytochrome P450 systems (CYPs) are the main enzymes involved in drug metabolism, phytomedicine and xenobiotics; the majority of drugs interact with the CYP3A isoform. *Echinacea purpurea* (Echinacea) has been shown to significantly induce CYP3A (Oga *et al.,* 2016). Transport proteins are also useful drug targets.

1.11.2.2.1 Pharmacokinetics

Pharmacokinetics determine the speed and duration of drug exposure to target organs (Holford, 2024). Drug elimination occurs through the kidneys and liver, with hepatic clearance being a significant factor. Alterations in drug pharmacokinetics can lead to changes in drug concentrations, affecting efficacy and toxicity (Holford, 2024). Chemotherapeutic agents and certain targeted therapies are associated with the highest risk of interactions in cancer therapy (Jermini *et al.,* 2019). Alterations in drug pharmacokinetics, including changes in maximum drug exposure and therapeutic intervals, can have significant consequences. Increased drug concentrations can enhance efficacy but also increase the risk of toxicity. Conversely, induction of drug metabolism can lead to decreased drug concentrations, resulting in reduced therapeutic effectiveness. These interactions can have a profound impact on treatment outcomes and patient safety, highlighting the importance of careful consideration and monitoring of drug interactions in cancer therapy (Knecht *et al.,* 2020).

1.11.2.2.2 Pharmacodynamics

Pharmacodynamics refers to the effects of drugs on the body (Niu *et al.,* 2019). When pharmacodynamic interactions occur, this may result in a synergistic effect (additive) or antagonistic effect of the co-administered drug (Niu *et al.,* 2019). Synergistic interactions

lead to the potentiation of the effects of the synthetic molecule. Herbal medicines or CAMs can interact with allopathic medicine and result in unwanted effects (Surana *et al.,* 2021). Adverse effects from CAM use may mimic or enhance the adverse effects experienced when using conventional anticancer therapy. Treating physicians unaware of CAM use in cancer patients may reduce the dose or halt anticancer treatment to manage these adverse effects (Firkins *et al.,* 2018). Patients considering CAMs should be aware of the herb-drug interactions for their own safety (Surana *et al.,* 2021).

1.11.3 Research problem

There is a lack of knowledge regarding the prevalence of CAM use in South African cancer patients. The diverse population of South Africa, known for its cultural differences, makes it necessary to determine the incidence of CAM usage amongst cancer patients. This data on CAM use in cancer patients may help to address potential risks associated with CAM use and improve patient outcomes. This study will provide baseline data to address this knowledge gap.

1.11.4 Study aim and objectives

The aim of the study is to describe the prevalence and identify specific CAMs used by cancer patients receiving chemotherapy at an academic hospital in Johannesburg.
The objectives of the study are to

- identify and categorise the types of CAMs used by patients.
- To identify the potential risk or harm specific CAMs pose to the patients on treatment.
- Describe the available scientific literature regarding potential drug-CAM interactions.

To meet the objectives of the study, the study was conducted in two parts. Part One entails a researcher-administered questionnaire, and Part Two is a traditional literature review of the selected CAMs to identify risks posed to cancer patients.

1.12 Summary

Chapter One provided an introduction to this study as well as a literature review. Chapter Two will focus on the research design and methods.

1.13 Chapter division

This dissertation consists of the following five chapters:

Chapter One: Literature review

Chapter Two: Research design and methods

Chapter Three: Results

Chapter Four: Literature review on selected CAMs

Chapter Five: Discussion and conclusion

2 CHAPTER TWO
RESEARCH DESIGN AND METHODS

2.1 Introduction

Chapter One provided an introduction to the study, outlining its rationale and objectives. Chapter Two describes and justifies the research design and methods employed in the study, including the systematic approach utilised in selecting the research design and methods.

2.2 Research design

The research design refers to the procedures undertaken to collect the relevant data, the methods applied to analyse the collected data, as well as how the findings address the research question (Boru, 2018). This study utilised a descriptive design, incorporating both cross-sectional and literature review approaches. The descriptive design enables the depiction of characteristics or circumstances through frequency analysis (Brink *et al*., 2022), allowing for the identification of prevailing trends in CAM usage among cancer patients in South Africa, where local data is limited.

The cross-sectional approach, employed in Part One, provides a snapshot of CAM use among cancer patients at a specific point in time, enabling the examination of variables relevant to the research within a population sample (Brink *et al.,* 2022).

Part Two of the study involves a traditional literature review, using a systematic approach to search the literature. This process is aimed to identify documented risks associated with the identified CAMs. “This entails a comprehensive, critical and objective analysis of the current knowledge on the topic” (Charles Sturt University Library, 2024).

2.3 Research methods: Part One of the study

Research methods are described as specific procedures and techniques utilised to identify, select, process, and analyse information about the research topic (University of the Witwatersrand, 2023). The following section provides an overview of the research approach, setting, population, and sampling strategies employed. This is followed by a detailed description of the data collection process, the data collection instrument utilised, and the data management and analysis procedures implemented to ensure data quality and integrity.

2.4 Research approach

A quantitative research approach was used, considering this is a robust methodology employed to investigate phenomena through the collection and analysis of numerical data. This approach enables researchers to test hypotheses, predict outcomes, and generalise findings to larger populations. The utilisation of questionnaires allows investigators to gather objective, reliable, and valid data. Statistical analysis of this data facilitates the identification of patterns, correlations, and causal relationships, providing valuable insights into the research question (Ghanad, 2023).

2.4.1 Research setting

The research setting refers to the location or site where data collection will take place (Brink *et al.*, 2022). The research setting for this study is situated at a prominent academic hospital located in Johannesburg, South Africa. This tertiary and quaternary care facility is one of the ten central hospitals in the country, providing specialised services and ranking among the largest healthcare institutions in the Gauteng region (Gauteng Provincial Government, 2022). The hospital offers comprehensive cancer treatment services, including medical and radiation oncology (South African Government News Agency, 2014). The medical oncology unit is equipped with thirty-two specialised chairs dedicated to the administration of cancer chemotherapy and monitoring of patients receiving cancer treatment (Meyer, 2021).

2.4.2 Population, sampling and recruitment

The study population is defined as the population accessible to the researcher (Brink *et al.,* 2022). The study population comprised a specific group of individuals meeting the research criteria, namely outpatients at the designated study site with a previous or current cancer diagnosis receiving cancer chemotherapy or radiation therapy during the data collection period.

The calculated sample size of n=120 was the minimum sample to achieve precision and accuracy and was based on an 80% CAM use prevalence (Subramani & Lakshmanaswamy, 2017), with a margin of error of 5% and a 95% confidence interval (CI). The sample size was calculated using Fisher's Sample formula: n = Z2 x (P) X (1-

P) / d2 where Z is a constant of 1.96; P is the expected prevalence or incidence; d is the margin of error set at 5%. Statistical significance was set at a value of p≤0.05.

Convenience sampling, also known as availability sampling, was employed, selecting participants readily available in the research setting (Brink *et al.,* 2022). Patients meeting the inclusion criteria (aged 18 years or older receiving cancer chemotherapy) were approached in the waiting area of the Academic Hospital's Medical Oncology Unit during their scheduled appointments or treatment. Recruitment and data collection took place from April to December 2022, continuing until the desired sample size was achieved.

2.4.3 Data collection method and instrument

Data collection is the systematic process of gathering information to address the research question (Brink *et al*., 2022).

The data were collected using a researcher-administered questionnaire (Appendix 1). The questionnaire was completed with the assistance of a field worker, who was a PhD student in the Pharmacology Department at that time. This data collection instrument comprised both open- and closed-ended questions. The questionnaire's development was informed by a thorough review of published literature, drawing on established tools and guidance from researchers in the field (Humpel & Jones, 2005; Ezeome & Anarado, 2007; Quant SA *et al.,* 2009; Bryden & Browne, 2016; Beretta *et al.,* 2017; Lee *et al.,* 2019). Furthermore, the questionnaire was subject to review by the study supervisors, ensuring its validity and reliability in capturing the requisite data. The questionnaire was divided into three sections to gather comprehensive data. Section one focused on capturing patient demographics, including sex, age, educational level, home language, and employment status. Section two elicited information on patient characteristics, encompassing cancer diagnosis, disease stage, and treatment modalities for disease and symptom management. Section three aimed to investigate the prevalence and distinctive features of CAM usage among the study population. The questionnaire was initially developed in English and subsequently translated into isiZulu based on the linguistic demographics reported by Khanyile and Ballard (2022), which indicated that isiZulu is the most widely spoken language in Gauteng households, followed by Sesotho, Sepedi, and English.

Pre-testing of the instrument was completed on ten respondents. Pre-testing allows the identification of possible flaws in the instrument but also supports the researcher in determining the logical arrangement of the data collection technique (Brink *et al.*, 2022). Following pre-testing, minor revisions were made to the questionnaire, including the rewording of questions (e.g., question 7: "diagnosis" was expanded to "diagnosis and stage of disease, if known"), the addition of a "not applicable" option in the CAM use section and the inclusion of question 10, which pertains to participants' consideration of CAM use despite not currently using it.

The data collection process was executed as follows:

- Upon obtaining all necessary hospital and ethical clearances, the support of the Head of Department and unit staff of the medical oncology unit was secured.
- Patients were recruited in the waiting area while awaiting medical consultation or treatment.
- The researcher and field worker introduced themselves and provided a comprehensive overview of the research project, utilising an information leaflet.
- Voluntary participation and informed consent requirements were emphasised, and the informed consent form was employed to obtain consent and explain the request for access to medical records, in which case the patient could accept or decline access.
- Willing participants were escorted to a private area in the waiting room between 6:00-9:00 am, ensuring confidentiality and privacy. Privacy and confidentiality could be maintained because of the unoccupied waiting room and the number of vacant seats. Patients are managed on a first-come, first-serve basis, and therefore, participants were asked to remain in the waiting area to prevent them from forfeiting their position in the line-up.
- Written consent was obtained before initiating data collection. In instances where completion of the questionnaire was interrupted due to medical consultation or treatment, the questionnaire was either completed on an alternative day or excluded from the final dataset.

- When participants were uncertain about their diagnosis or treatment details, this information was verified through their hospital files, with the participants' permission.

2.4.4 Data management and analysis

The completed questionnaires were placed in a concealed box. Each questionnaire was assigned a unique identifier in sequential order and entered on an Excel spreadsheet. Data processing of the questionnaires was carried out in three stages that involved data sorting, data cleaning and storage of the data. These functions were achieved by making extensive use of Microsoft Excel 2010. Refining of the data and results was required for the final data report (Brink *et al.*, 2022). Identification and listing of the most commonly used CAMs allowed the analysis and a comprehensive literature search to be done on these CAMs. These results are documented in Chapter Four of this dissertation.

The data from each questionnaire was entered into a Microsoft Excel spreadsheet for analysis purposes. The Excel spreadsheet was organised into horizontal and vertical configurations. The horizontal configuration was organised into fixed columns, each column representing a question in the questionnaire. The vertical configuration was organised based on the level of information provided by the participant. The format was used to make it possible to import the data into IBM SPSS version 29.

After the completion of data collection, data were checked for completeness, edited, cleaned and exported to IBM SPSS version 29 for analysis. Descriptive statistics were used to describe the patient demographics, disease and treatment characteristics of the sample as well as CAM use. This included frequency distributions, age ranges and means. Descriptive statistics summarise the characteristics of a data set (Brink *et al*., 2022). The summarised and organised data allows simplified and explanatory interpretation. Systematic representation of the data allows for accurate reporting and clear identification of the proportion of participants administering CAMs while on cancer chemotherapy (Brink *et al.,* 2022).

Inferential statistics were used to investigate the significance of the relationships between variables (Brink *et al.,* 2022). This is to identify whether the difference in the means is by

chance or is significant (Brink *et al.,* 2022). IBM SPSS software suite for data management was used for statistical analysis. The level of significance was set at a p-value of 0.05 as a cut-off point. In order to determine whether the relationship between two categorical variables is significant, the chi-square statistic was calculated.

2.4.4.1 Validity, reliability and efficiency

Content validity refers to the degree of accuracy with which the instrument represents all components of the variable to be measured or studied (Brink *et al.*, 2022). Content validity was enhanced by reviewing the literature for similar instruments. Reliability, defined as the consistency of results across multiple administrations by different researchers, was maximised through the use of a structured questionnaire with predetermined response options (Brink *et al.*, 2022). Reliability was enhanced in that respondents were asked the same questions with a list of possible answers to be selected. Clarifications were provided when required. The field worker involved in the study captured the responses in a similar manner to the researcher. Moreover, the instrument demonstrated efficiency, requiring minimal resources and effort while yielding valid and reliable data (Brink *et al.,* 2022). The ease of use and cost-effectiveness of the instrument further enhanced its efficiency.

2.5 Part Two of the study: Literature review

Employing a thorough search of the literature, this traditional literature review focused on identifying systematic reviews, meta-analyses, and primary literature from the past five years, whenever possible. This approach enabled a thorough investigation of the most commonly used CAMs and their potential interactions, efficacy, and safety in the context of cancer treatment. A systematic approach was used, and multiple databases, such as MEDLINE (via PubMed), EMBASE, Science Direct, Scopus and Cochrane library. Specific search terms utilised included, but were not limited to, “Superlife STC30 AND cancer”, “Superlife STC-30 AND chemotherapy“, “Vitamin C AND/OR Cancer”, ”Vitamin C and chemotherapy interactions”, “Ascorbic acid AND/OR Cancer”, “Cancer bush / Kankerbos *(Sutherlandia frutescens)”* AND/OR “Cancer”, “Cancer bush herb-drug interactions”, “Grape Seed Extract’ AND/OR Cancer”, “Dietary supplements AND/OR vitamins drug interactions in cancer”, “Bicarbonate of Soda AND/OR Cancer”, “Ginger

AND/OR Cancer", "Rooibos tea *(Aspalathus linearis)* AND/OR Cancer", "Cannabis AND/OR Cancer".

2.6 Ethical considerations

The study applied the fundamental ethical principles for research guided by the Declaration of Helsinki. The protection of participants' rights, respect and fair selection of participants, as well as participants' right to privacy and voluntary participation, was applied (World Medical Association, 2013).

The following measures were implemented:

- The research proposal was presented to the Department of Pharmacology and the University Postgraduate Committee for review. Approval led to the proposal submission for Human Research Medical Ethics clearance by the Institutional Review Board, Human Research Ethics Committee of the University of the Witwatersrand.
- The Human Research Ethics Committee of the University of the Witwatersrand granted ethical clearance (Reference No: M210803) on 24/02/2022 (Appendix 2). A signed copy was provided as requested by the committee.
- Furthermore, permission was acquired in order to conduct the research from the Gauteng Department of Health as well as the Gauteng Chief Executive Officer of the academic hospital (Appendix 3).
- The Head of Department of the Medical Oncology Unit provided acknowledgement and approval prior to the commencement of the study (Appendix 4). The researcher was made aware of the appointment of a new Head of Department at the Medical Oncology Unit, and therefore, verbal consent was obtained upon the provision of all relevant approval and permission documentation.
- All respondents were informed of their voluntary participation in the study and their right to privacy and confidentiality. The researcher welcomed questions at any point and explained to the participants their rights to withdraw at any time and their right to refuse or disclose information. The information leaflet (Appendix 5) describing the nature of the study was given and explained to each participant.

The informed consent (Appendix 6) was provided and explained to the participants willing to partake in the research.

- Adherence to the principle of beneficence required the researcher to ensure all participants were protected from any discomfort, including any emotional distress. In this study, there was no foreseen physical, emotional, psychological, economic, social or legal harm as a result of the participation in this study. A distress protocol was in place for participants reporting any feeling of discomfort. The protocol included immediate termination of the data collection process. The information sheet provided to the participant included information on support or counselling services provided by a counsellor, with the relevant contact details of the counsellor. The counsellor's permission was granted prior to the study initiation. None of the respondents had any emotional discomfort as a result of the questions posed nor required or requested counselling. Respondents were provided with an opportunity to ask questions and express their feelings to the researcher.
- Each participant involved in the research has the right to expect that any information collected from or about the participant remains anonymous and confidential. The participants also have the right to decide to what extent or circumstances their private information can be shared; this includes beliefs, medical records, behaviours and opinions (Brink *et al.,* 2022). The respondents were reassured that in the published data, anonymity would be maintained, and responses, as well as consent forms, would be stored in a secure location. These scenarios were discussed when seeking consent for participation. Anonymity has been added to all responses by the researcher.
- The study participant information may be recorded, managed and stored to allow accurate reporting, analysis, interpretation and verification or validation (Department of Health, 2020). The completed questionnaires are filed and stored at the Pharmacology Department of the University of the Witwatersrand in an access-controlled, locked cabinet. Accessibility is limited to the researcher and supervisors only and for not less than ten years in accordance with the document retention period according to the guidance from SAHPRA (Department of Health South Africa, 2020). The Microsoft Excel datasheets are stored on the researchers'

password-protected computer in alignment with the necessary confidentiality and backup requirements.

- Dissemination of the study results should be done in a timeously, accessible and responsible manner. This includes engaging participants, communities or key role players involved in the research process (Department of Health South Africa, 2020). The dissertation will be provided to the oncology unit, and the results will be presented in a table format for all key role players to access before year-end 2024.

2.7 Summary

Chapter Two comprehensively presented the research design and methods employed in this study. The research setting, population, and sampling strategy were thoroughly described, followed by a detailed explanation of the data collection instrument, data collection procedures, data analysis techniques, and measures taken to ensure data validity and reliability. Additionally, ethical considerations were addressed. The subsequent chapter (Chapter Three) presents a comprehensive overview of the study's findings, providing a detailed account of the results yielded by this study.

3 CHAPTER THREE
RESULTS

3.1 Introduction

Chapter Two discussed the research methods employed in the study. Chapter Three presents the results of the study, which encompasses an overview of patient demographics, disease characteristics and treatment modalities, as well as the prevalence and distinctive features of CAM usage among the study population.

3.2 Patient demographics

This study represents data collected from 120 respondents (n=120). The respondents' ages ranged between 19 and 79 (mean age of 51 years). The gender distribution showed that 74.2% (n=89) of the respondents were females, with males comprising 25.0% (n=30). English (24.2%; n=29) and isiZulu (20%; n=24) were the most prevalent languages spoken amongst the respondents. Educational level varied, with 55% (n=66) of respondents having completed secondary schooling, 18.3% (n=22) having completed tertiary or higher education, (26.7%; n=32) having achieved an educational level between grades ten and lower. The unemployment rate of the respondents was 59.2% (n=71). Table 3.1. displays the demographic characteristics of the patient population along with corresponding p-values which indicate the statistical significance of the associations between these variables and CAM use.

Table 3.1 Patient demographics (n=120)

Patient Demographics	N (%)	CAM Users (%)	CAM Non-users (%)	*P* value
Age				
Age (mean)	120 (100%)	51.28	51.28	0.880
Gender				
Male	30 (25%)	6 (20%)	24 (80%)	0.068
Female	89 (74.2%)	34 (38.2%)	55 (61.8%)	
Other	1 (0.8%)			
Home Language				
Afrikaans	16 (13.3%)			n/a
Amharic	1 (0.8%)			
English	29 (24.2%)			
French	1 (0.8%)			
Igbo	3 (2.5%)			
Ndebele	3 (2.5%)			
Portuguese	1 (0.8%)			
Sepedi	2 (1.7%)			
Setswana	12 (10%)			
Sesotho	10 (8.3%)			
Tsonga	5 (4.2%)			
Venda	4 (3.3%)			
IsiXhosa	9 (7.5%)			
IsiZulu	24 (20%)			
Educational Level				
Grade 10 and lower	32 (26.7%)	13 (40.6%)	19 (59.4%)	0.141
Grade 11-12	66 (55%)	17 (25.8%)	49 (74.2%)	
Tertiary	22 (18.3%)	10 (45.5%)	12 (54.5%)	

Patient Demographics	N (%)	CAM Users (%)	CAM Non-users (%)	*P* value
Employment Status				
Employed	49 (40.8%)	15 (30.6%)	34 (69.4%)	0.599
Unemployed	71 (59.2%)	25 (35.2%)	46 (64.8%)	

*Note: Statistically significant, p≤0.05; CAM: Complementary and Alternative Medicine

3.3 Disease and treatment characteristics

The disease characteristics of the patient population are succinctly presented in Tables 3.2 and 3.3. A majority (54.2%; n=65) of the patients were diagnosed with breast cancer, followed by gastrointestinal cancers (15.8%; n=19). Haematological malignancies accounted for 15.8% of cancer diagnoses, with lymphoma being the most prevalent (8.3%; n=10), followed by leukaemia (6.7%; n=8) and multiple myeloma (0.8%; n=1). These findings highlight the distribution of cancer types within the study population.

Table 3.2 Respondent reported disease diagnosis (n=120)

Disease Characteristics		
Diagnosis	**n**	**%**
Breast cancer	65	54.2
Breast cancer & ovarian cancer	1	0.8
Ovarian cancer	3	2.5
Cervical cancer	2	1.7
Choriocarcinoma	1	0.8
Prostate cancer	2	1.7
Colorectal cancer	10	8.3
Gastric cancer	5	4.2
Gastro-oesophageal cancer	1	0.8
Liver cancer	1	0.8
Pancreatic cancer	1	0.8
Sarcoma	4	3.3
Lung cancer	2	1.7
Thyroid cancer	1	0.8
Skin cancer	1	0.8
Multiple myeloma	1	0.8
Leukaemia	8	6.7
Lymphoma	10	8.3
Missing data	1	0.8
Total	**120**	**100**

3.3.1 Tumour staging

Among the total respondents (n=120), only 41% (n=50) had or provided information on their cancer staging. The available information revealed that 35.83% (n=43) had advanced disease (Stage 3 or 4), with a notable 86% presenting with advanced or metastatic disease (Stages III-IV). Conversely, 59% (n=70) lacked staging information;

this was reported as missing information. Among those with known staging, only 5.83% (n=7) had early-stage cancer. Specifically, one lymphoma respondent had Grade I disease, while those with myeloid leukaemia (n=7) and non-Hodgkin's lymphoma (n=1) had chronic and high-grade disease, respectively.

Table 3.3 Stage of disease (n=120)

Stage of Disease	**n**	**%**
Solid Tumours		
Stage I	1	0.8
Stage II	6	5.0
Stage III	12	10.0
Stage IV	31	25.8
Missing data	61	50.8
Haematological Malignancies		
Grade I	1	0.8
High grade	1	0.8
Chronic	7	5.8
Total	**120**	**100**

3.4 Cancer chemotherapy and radiation therapy

All respondents (100%; n=120) reported receiving cancer chemotherapy or anticancer treatment inclusive of radiation therapy as part of their cancer treatment. Radiation therapy was reported in terms of the number of sessions. Only two respondents reported active or completed radiation therapy.

Chemotherapeutic agents' administration specifically was reported in terms of treatment cycles; respondents reported or had documented evidence of varying numbers of completed treatment cycles, ranging from one (6.7%; n=8) to nine (0.8%, n=1). Prescribed hormone therapy is presented in Table 3.6, and targeted therapy used as cancer chemotherapy is discussed below. These findings highlight the variability in treatment duration and modality among the respondents.

Table 3.4 Chemotherapy treatment cycles (n=79)

Chemotherapy Treatment Cycle	n	%
1	8	10.1%
2	11	14.0%
3	11	14.0%
4	9	11.4%
5	6	7.5%
6	11	14.0%
7	4	5.0%
8	2	2.5%
9	1	1.2%
Missing information	16	20.3%
Total	**79**	**100%**

3.4.1 Chemotherapeutic agents

Chemotherapeutic agents disclosed in Figure 3.1 were reported or documented as monotherapy or as a combination of chemotherapeutic drugs. The most frequently used agent was capecitabine (10%; n=12), followed by paclitaxel (9.17%; n=11).

Table 3.5 Chemotherapeutic drugs prescribed to patients (n=120)

Chemotherapeutic Agents	n	%
Anthracycline, Cyclophosphamide	4	3.3
Anthracycline, Cyclophosphamide, Paclitaxel	1	0.8
Anthracycline, Docetaxel	1	0.8
Adriamycin (Doxorubicin), Vincristine, Bleomycin	1	0.8
Cyclophosphamide, Docetaxel	4	3.3
Cyclophosphamide, Doxorubicin, Vincristine	6	5.0
Cyclophosphamide, Vincristine	2	1.7
Docetaxel	5	4.2
Docetaxel, Carboplatin	4	3.3
Docetaxel, Fluorouracil, Oxaliplatin	2	1.8
Capecitabine	12	10.0
Capecitabine, Oxaliplatin	5	4.2
Capecitabine, Irinotecan	1	0.8
Capecitabine, Carboplatin/Gemcitabine	1	0.8
Capecitabine, Epirubicin, Oxaliplatin	1	0.8
Carboplatin, Paclitaxel	4	3.3
Doxorubicin	1	0.8
Gemcitabine	1	0.8
Gemcitabine, Cisplatin	1	0.8
Gemcitabine, Carboplatin	9	7.5
Gemcitabine, Nab-paclitaxel	1	0.8
Gemcitabine, Oxaliplatin	1	0.8
Paclitaxel	11	9.2

Chemotherapeutic Agents	n	%
None	31	25.8
Missing data	10	8.3
Total	**120**	**100**

3.4.2 Targeted therapy and modulators of protein degradation

The most commonly used targeted therapies were trastuzumab and imatinib, each prescribed for 6.67% (n=8) of the population. Rituximab was used by 5% (n=6) of respondents and nilotinib by 1.7% (n=2). Thalidomide was prescribed for only one patient (0.8%; n=1). The combination of vemurafenib and rituximab was also used as a treatment regimen. However, for the majority of respondents (78.3%, n=94), these targeted therapies were either not prescribed or not reported.

3.4.3 Hormone therapy

Table 3.6 Prescribed oestrogen and progesterone inhibitors and antagonists (n=120)

Hormone Therapy	n	%
Anastrozole	6	5.0
Bicalutamide	1	0.8
Goserelin, Bicalutamide	1	0.8
Letrozole	1	0.8
Tamoxifen	17	14.2
Tamoxifen, Goserelin	3	2.5
Missing data	11	9.2
None reported (NR)	80	66.7
Total	**120**	**100**

3.4.4 Other agents

The reported prescribed therapies, tailored to individual patient needs, encompass a broad range of pharmacological classes listed in Table 3.7.

Table 3.7 Other agents prescribed for cancer patients' individual needs

Agent	Indication for Use*
Acyclovir	Treatment of herpes simplex and varicella-zoster viruses, prophylaxis of frequent recurrent episodes of herpes genitalis
Allopurinol	Long-term treatment of primary or secondary hyperuricemia
Dexamethasone	Anaphylaxis, cerebral, oedema, management of allergic and inflammatory disorders.
Fexofenadine hydrochloride	Treatment of allergic conditions, anaphylaxis

Granulocyte colony stimulating factor	Acceleration of neutrophil count recovery in clinical situations with severe neutropenia, minimizing the risk of infections, neutropenia associated with myelosuppressive chemotherapy for solid and haematological malignancies, drug –induced, idiopathic and HIV-associated neutropenia. Mobilization of stem cells before stem cell transplant
Iron sucrose	Treatment of iron severe iron deficiency in adults not responding to oral iron therapy
Lactulose	Treatment of acute and chronic constipation, also used in hepatic ecelophalopathy
Lansoprazole	Management of Gastro-oesophageal reflux diseases and dyspepsia, also eradication of *H. pylori*
Levothyroxine	Treatment of hypothyroidism
Loperamide	Treatment of acute and chronic diarrhoea
Metoclopramide	Prevention of post-operative nausea and vomiting, radiotherapy-induced nausea and vomiting, delayed (not acute) chemotherapy-induced nausea and vomiting
Omeprazole	Management of gastric and duodenal ulcers, reflux oesophagitis and Zollinger-Ellison syndrome, eradication of *H. pylori*
Ondansetron	Management of nausea and vomiting induced by chemotherapeutic agents and radiotherapy, prevention of post-operative nausea and vomiting
Prednisone	Management of allergic and inflammatory disorders
Promethazine	Management of allergic reactions, preferred for management of acute anaphylaxis, prevention and treatment of nausea and vomiting
Calcium carbonate	Relief of dyspepsia and treatment of reflux oesophagitis
Venlafaxine	Treatment of major depressive disorders, depression associated with anxiety, general anxiety disorder
Vitamin D and calcium	Correction of abnormalities in calcium and phosphate metabolism in renal osteodytrophy. Treatment of osteoporosis
Zoledronic acid	Treatment of tumour-induced hypercalcemia, osteolytic metastases in myeloma, Paget's bone disease, osteoporosis, even glucocorticoid-induced osteoporosis

*Indication for use as per The South African Medical Association, 2024

3.5 Prevalence and characteristics of Complementary and Alternative Medicine use

CAM usage was reported by a third of respondents (33%; n=40), while the majority (66.7%; n=80) did not utilise CAMs. Among the CAM users, 16 individuals reported using multiple CAMs, resulting in 79 CAMs being reported by 33.3% (n=40) of the respondents. Notably, 21.66% (n=17) of non-CAM users (n=80) had previously considered using one or multiple CAMs, with cannabis, CBD oil, herbs, and vitamin supplements being among the considered products. Pineapple and aloe boiled in water, green tea, papaya seeds, vitamin supplements such as vitamin B12, Beta Guard), fresh ginger and lemon or juiced fruits and vegetables consisting of carrots, spinach, apples and lemon were also reported. A select number of respondents failed to mention a specific product or failed to recall a product name. Respondents' motivation or rationale for using CAMs is presented in Table 3.9.

Table 3.1 presents a summary of patient demographics and their potential association with CAM. Chi-square analysis indicated that sex as a variable for CAM use (male vs. female) showed no significant association ($p = 0.068$). Furthermore, the relationship between level of education and CAM use was found to be non-significant ($p = 0.141$), as was employment status ($p = 0.599$). These findings suggest that patient demographics, including age, sex, education level, and employment status, do not have a significant impact on CAM use, indicating a lack of association between these variables.

Table 3.8 Complementary and Alternative Medicine (CAM) users and non-users (n=120) based on type of cancer

Disease Characteristic	Total Patient Numbers		CAM Users		Non-users of CAM		*P* value
Diagnosis	n	%	n	%	n	%	
Breast Cancer	66	55.0	24	60	42	52.5	0.027
Female Reproductive Organ Cancer	6	5	3	7.5	3	3.8	1.0
Gastro Intestinal Cancer	18	15	5	12.5	13	16	0.059
Lung Cancer	2	1.8	1	2.5	1	1.3	1.0
Haematological Cancer	19	15.8	5	12.5	14	17.5	0.039
Medullary Thyroid Cancer	1	0.8	1	2.5	0	0	n/a
Skin Cancer	1	0.8	0	0	1	1.3	n/a
Prostate Cancer	2	1.8	0	0	2	2.5	n/a
Sarcoma	4	3.3	1	2.5	3	3.8	0.317
Unknown	1	0.8	0	0	1	1.3	n/a
Total	**120**	**100**	**40**	**100**	**80**	**100**	

*Note: Statistically significant, p≤0.05

The data analysis revealed a statistically significant association between CAM use and specific cancer diagnoses. Specifically, respondents with breast cancer (p = 0.027) and haematological cancers (p = 0.039) demonstrated a significantly higher likelihood of using CAMs compared to patients with other cancer diagnoses. This is presented in Table 3.8.

3.5.1 Complementary and Alternative Medicines reported

The CAMs reported consisted of nutritional practices or biologically based products as well as other CAM practices. Table 3.9 provides an overview of the reported, the frequency at which each CAM was reported, the formulation in which the complementary medicine is consumed and the participant's rationale for use. The CAMs are grouped based on the product constituents.

Table 3.9 Biologically-based Complementary and Alternative Medicine (CAM) reported frequency, formulation and rationale for use

CAM	Frequency	Formulation	Rationale for Use
(i) NUTRITIONAL OR BIOLOGICALLY BASED CAMs			
A) FRUITS (FRESH FRUITS, LEAVES, SEEDS AND FRUIT EXTRACTS)			
Lemon	3	Fresh lemon, lemon juice	Enhances the immune system and relieves nausea
STC30-Superlife	2	Powder	Increase energy levels
Procydin/ Grape seed extract *(Vitis vinifera)*	2	Capsule	Increase energy levels and enhances the immune system
Berries	1	Unknown	Anti-oxidant effect
Red wine	1	Liquid	Unknown
Coffee enema	1	Liquid	Unknown
Papaya, mango and avocado leaves	1	Unknown	Purification of blood and cancer fighting
B) VEGETABLES, VEGETABLE LEAF EXTRACTS AND VEGETABLE JUICES			
Vegetable juice	2	Juice	Antioxidant against chemotherapy, enhances the immune system and fight cancer cells
Beetroot	1	Juice	Immune boosting

CAM	Frequency	Formulation	Rationale for Use
C) HERBS, HERBAL EXTRACTS AND HERBAL TEAS			
Herbal teas Rooibos tea Green tea Ginger tea Unknown	9 (4) (2) (2) (1)	Teas	Hydration, supports healthy bowel movements, enhances the immune system, taste sensation and relieves nausea
Ginger	5	Fresh ginger, pickled ginger	Enhances the immune system and relieves nausea
Turmeric	3	Powder	Destruction of cancer cells
Garlic	2	Fresh	Enhances the immune
Intervene herbal	1	Powder	Unknown
Herbal laxative	1	Tablet	Relieves constipation
Coa-mixture	1	Liquid	Enhances appetite
D) MEDICINAL PLANTS AND MEDICINAL PLANT EXTRACTS OR SEEDS			
Cannabinoids and cannabis	8	Oil (drops), capsule, leaves (smoke)	Pain relief, relieves nausea, enhances the immune system, calming and anticancer activity
Cancer Bush *(Sutherlandia frutescens)*	2	Tea or powder	Decrease tumour size, cancer fighting and alleviate pain
Black seed	1	Seeds	Blood purification and anticancer activity
Aloe	1	Mixed with water	Blood purification and anticancer activity
Glyconutrients	1	Capsule	Enhances the immune system and cancer fighting

CAM	Frequency	Formulation	Rationale for Use
E) VITAMINS, MINERALS AND DIETARY SUPPLEMENTS			
Multi-vitamin	8	Tablet	Recommended daily allowance, enhances energy levels and immune system, for hormones
Vitamin C *(ascorbic acid)*	5	Tablet or effervescent	Enhances the immune system and replenishing cancer draining of vitamin C
Vitamin B includes Vit B9 and B12	5	B9 - tablet B12 - subcutaneous injection	Enhances the immune system Enhances energy levels
Omega-3	1	Capsule	Enhances the immune system
Zinc	1	Tablet	Limiting the cancer growth and spread
Vitamin D	1	Tablet or capsule	Enhances the immune system
Cellfood	1	Drops	Purifies blood and cancer fighting
Cod Liver oil	1	Capsule	Unknown
(ii) OTHER COMPLEMENTARY PRACTICES AND COMPOUNDS			
Bicarbonate of soda	1	Tablets	Prevention and treatment of cancer
A. Vogel Multiforce® alkaline powder	1	Powder	pH balance
Sweat Libido Booster	1	Capsule	Enhance libido
Milk stout	1	Liquid	Unknown
dōTERRA oil	1	Oil (drops)	Increases blood cell count
Kelp	1	Tablet	Increases iodine
Chinese medicine	1	Tablet	Unknown
Total	**79**		

3.5.2 Complementary and Alternative Medicine use: frequency, amount and formulation

The respondents who reported using CAMs (33%; n=40) demonstrated varying frequencies of use. The seventy-nine CAMs reported in totality were administered daily (59.5%; n=47), followed by seldom administration or use (11.4%; n=9), weekly use (8.9%, n=7), and frequent/often use (3.8%; n=3). Notably, 16.5% (n=13) of respondents were uncertain about the frequency of that specific CAM administration. The high daily usage rate was primarily driven by the consumption of herbal teas and supplements. The quantification of CAM use varied widely; besides the ‘general’ amount presented in Table 3.10, respondents reported usage in diverse units such as drops, enemas, litres of fluid, and leaves for hand-rolled cannabis cigarettes. Moreover, respondents employed CAMs in multiple formulations, with 27.8% reporting "other" formulations that encompassed liquids, juices, leaves, fresh or pickled products, seeds, and other forms. This highlights the diverse and creative ways in which respondents incorporated CAMs into their treatment regimens.

Table 3.10 Complementary and Alternative Medicine (CAM) use: amount and formulation (n=79)

CAM Use: Amount	**n**	**(%)**
Teaspoon	5	6.3%
Tablespoon	6	7.6%
Glass/Cup	19	24.1%
Tablet/Pill form	27	34.2%
Unsure	10	12.7%
Other	12	15.2%
CAM Use: Formulation	**n**	**(%)**
Tablet/Pill form	27	34.2%
Other	22	27.8%
Tea	10	12.7%
Smoke	3	3.8%
Oil	4	5.1%
Powder	4	5.1%
Injectable	1	1.3%
Unknown	8	10.1%

3.5.3 Sources of Complementary and Alternative Medicine information and suppliers

The information sources used by patients, which led to their CAM selection, were driven by the Internet (35.4%; n=28). Other sources of 17.7% (n=14) included broadcast media (television and radio), pharmacist and shop assistant recommendations, as well as habitual use. In addition to the above-reported information sources, respondents also acquired the information from friends (13.9%; n=11), family (8.9%; n=7), other patients (5.1%; n=4) and healthcare professionals (3.8%, n=3). The remaining (1.3%; n=8) included the church community (13.9%; n=11) and unknown.

The procurement of CAM products was facilitated by various sources, with 41.8% (n=33) of respondents obtaining them from diverse suppliers, including supermarkets, family members, online shopping platforms, street vendors, licensed cultivators, and product representatives. Additionally, pharmacies (36.7%; n=29), friends (2.5%; n=2), and traditional healers (1.3%; n=1) were also identified as suppliers. Notably, 17.7% (n=14) of respondents were uncertain about the source or identity of their CAM product suppliers. A detailed breakdown of the CAM suppliers and their corresponding frequencies, as reported by the respondents.

3.5.4 Respondents' perceptions of the efficacy of Complementary and Alternative Medicine

Table 3.11 Perceived efficacy of Complementary and Alternative Medicine (CAM) administered (n=79)

Effect	**n**	**%**
Yes	61	77.2%
No	6	7.6%
Unsure	12	15.2%
Total	**79**	**100%**

When asked about the perceived differences after using their preferred CAM, respondents reported a range of outcomes, including increased energy levels, enhanced immune function, cancer-fighting effects, decreased tumour size, softer breast tissue, improved blood flow, rehydration, pain and nausea relief, regular bowel movements, increased sexual drive and alleviation of chemotherapy-induced side effects. Additionally, some respondents reported increased appetite and a calming effect on sleep patterns, suggesting a potential impact on overall well-being. It is important to note that some of the reported outcomes may be attributable to the chemotherapy treatment rather than the CAM therapy but were nonetheless perceived by the patients as a direct result of their chosen CAM.

3.5.5 Disclosure or non-disclosure of Complementary and Alternative Medicine use

Among the respondents who reported using CAMs (33%; n=40), more than (52.0%, n=21) did not disclose this information to their treating oncologist or healthcare professional. In contrast, 45% (n=18) openly discussed their CAM use with their oncologist, while 2.5% (n=1) were uncertain whether they had disclosed this information. The reasons for non-disclosure were primarily reported as a lack of communication and inquiry by the oncologist regarding CAM use, insufficient consultation time, and respondents' perceptions of unnecessary disclosure. Additionally, some respondents reported fearing disclosure due to previous guidance from their oncologist advising against using any treatments beyond those prescribed.

3.6 Summary

Chapter Three presented the results of the questionnaire in terms of the three sections or categories. The next Chapter provides an overview of the literature investigating the potential risks associated with the use of selected CAMs in combination with cancer chemotherapy.

4 CHAPTER FOUR

LITERATURE REVIEW ON SELECTED COMPLEMENTARY AND ALTERNATIVE MEDICINES

4.1 Introduction

Chapter Four presents a literature review of the CAMs identified in Chapter Three and was selected for further investigation. To assess the potential risks associated with the selected CAMs, the following information will be discussed: CAM overview, claims related to selected CAMs, proposed anti-carcinogenic effects, formulation and quantity administered, known absorption, distribution, metabolism and excretion, as well as published evidence to determine CAM safety in cancer use.

4.2 Fruits, fresh fruits, leaves, seeds and fruit extracts

4.2.1 STC30-Superlife

STC30-Superlife, classified as an organic food supplement and "plant stem cell therapy", purports to manage a wide range of ailments, including cancer and leukaemia (Superlife South Africa, 2021). This falsely claimed “stem-cell” supplement evidently rejuvenates, regenerates and repairs damaged cells, tissues and organs by activating the body's stem cells. The supplement's constituents, as reported by Erhirhie *et al.* (2023), include (i) swiss apple, (ii) grapes, (iii) glisodin, (iv) bilberry, (v) blackcurrant juice powder and blueberry extract. According to the manufacturer, these ingredients supposedly work in synergy, aiming to promote cellular health and wellness.

4.2.1.1 Recommended formulation and consumption

The STC30-Superlife product is packaged in boxes containing 15 sachets, each filled with 1.5 g of dry powder, intended for daily sublingual administration. This route is recommended to avoid ingestion, as the product may undergo neutralisation when metabolised through the digestive system and liver enzymes (Superlife South Africa, 2021). This suggests that the bioactive compounds in the product may be susceptible to first-pass metabolism, which could reduce their efficacy.

4.2.1.1.1 Known toxicology information

To investigate the toxicity profile of STC-30 Superlife, Erhirhie *et al.* (2023) conducted in a 30-day repeated-dose toxicity study in Wistar rats. The results showed no signs of toxicity or mortality at a dose of 5000 mg/kg in the acute toxicity study. Repeated administration of the daily dose for 30 days did not produce toxic effects on haematology parameters, liver function (ALT, AST and ALP enzymes remained within normal ranges, indicating intact liver cells and tissue) and kidney function. However, administration of twice the recommended dose resulted in mild adverse effects on kidney and haematology parameters. Significant reductions were noted in the haematocrit, haemoglobin, red blood cell, and mean corpuscular haemoglobin concentration in the high-dose treatment group as compared to controls. Creatinine was also significantly decreased, suggesting that this supplement may pose a harmful effect on renal function when the polyherbal remedy is taken at double the recommended dose (Erhirhie *et al.,* 2023). These findings suggest that STC-30 Superlife might be tolerated at the recommended dose, but caution should be exercised when exceeding the recommended dose to avoid potential kidney and haematology-related adverse effects.

4.2.1.2 Product claims

Misleading claims and misinformation have been disseminated on social media, notably on the Superlife STC30 Philippines (2021) Facebook page, falsely stating that the product has received FDA approval. Additionally, the product has been deceitfully marketed as “stem cell therapy”, "all-natural", "clinically proven", "safe", and "curative" (Superlife South Africa, 2021). These claims are unsubstantiated and misleading, as they imply a scientifically supported efficacy and safety profile that has not been rigorously demonstrated. The product's proposed mechanism of action, which purportedly enables the creation of new cell structures and natural healing, lacks robust scientific evidence. Although a toxicological study was conducted in animal models (Erhirhie *et al.,* 2023), further rigorous clinical trials are essential to substantiate the safety and efficacy claims made by the manufacturer.

4.2.1.2.1 Health authority warnings on STC-30 Superlife

In November 2022, the Papua New Guinea Department of Health issued a public safety alert circular cautioning against the unauthorised marketing and medical use of unapproved “stem cell products”, specifically highlighting STC30-Superlife as the product of concern (Department of Health Papua New Guinea, 2020). This alert aimed to inform patients, healthcare practitioners (including conventional and alternative/traditional medicine practitioners), importers, retailers, and patient support groups about the illegal promotion and utilisation of these unapproved products. The circular warned of potential long-term risks associated with STC30-Superlife, as reported by the FDA and Therapeutic Goods Administration Australia, including blindness, life-threatening infections and malignant cell growth. Additionally, the Department of Health clarified that false claims had been made regarding the product's approval by drug regulatory authorities, emphasising that STC30-Superlife had not received the necessary regulatory approvals (Department of Health Papua New Guinea, 2020). This public safety alert aimed to protect public health and safety by disseminating accurate information and warning against the use of unapproved and potentially harmful stem cell products.

4.2.2 Grape seed extract *(Vitis vinifera)*

Grape Seed Extracts are derived from the seeds of *Vitis vinifera* seeds and comprise a mixture and various quantities of bioactive compounds such as catechin monomers, procyanidin oligomers and procyanidin polymers (Clouatre *et al.,* 2010). These extracts are often referred to by various names, including leucoanthocyanidins, oligomeric proanthocyanidins, procyanidins, procyanidolic oligomers and pycnogenols (Clouatre *et al.,* 2010). The commercial supplement available is marketed as Procydin.

A limited number of controlled studies have demonstrated the potential benefits of proanthocyanidins, specifically related to their antioxidant properties, immune-boosting effects and cardio-protective effects (Brasky *et al.,* 2011; National Center for Complementary and Integrative Health, n.d. b). Notably, a double-blind, randomised crossover trial conducted by Dinicola *et al.* (2014) found that supplementation with grape

seed extract resulted in a significant reduction in oxidative stress and an improvement in the glutathione/oxidised glutathione ratio in human subjects. Procyanidins present in grape seed extract have been reported to exert a protective effect against drug- and chemical-induced multi-organ toxicity (Darweesh *et al.,* 2020). The bioactive components in grape seed extract act as reducing agents and hydrogen-donating antioxidants, attributed to their polyphenolic structure. The polyphenol content in grape seeds varies depending on the grape variety, with seeds containing approximately 4% of the total seed weight and around 10% of the extractable phenolic substances in the berry. Notably, red wine is also a rich source of grape seed extract procyanidins, which are extracted into the wine during prolonged skin and seed contact during the winemaking process (Clouatre *et al.,* 2010).

4.2.2.1 Formulation and administration of Vitis vinifera grape seed extracts (Procydin)

According to the product information provided by Pharmacy Direct (n.d.), each Procydin tablet has a composition of (i) proanthocyanidins (70 mg), (ii) calcium ascorbate (30 mg), (iii) bioflavonoids (30 mg) and (iv) 15 mg vitamin E.

4.2.2.2. Preclinical and clinical antineoplastic and carcinogenic preventative properties of grape seed extracts

Pre-clinical studies, including in vivo and in vitro experiments, have demonstrated that grape seed extract and its constituents exhibit antineoplastic properties, characterised by induction of apoptosis (programmed cell death), anti-proliferative effects and direct cytotoxicity in various cancer cell lines (Kaur *et al.,* 2009). Furthermore, the flavonoids present in grape seed extract supplements have been shown to downregulate the expression of interleukin-6 (IL-6) and partially inhibit nuclear factor-κB signalling (Brasky *et al.,* 2011). Animal studies have also confirmed that grape seed extracts interfere with different stages of carcinogenesis and may exhibit an aromatase-inhibiting effect, leading to decreased oestrogen synthesis and increased androgen precursors (Clouatre *et al*., 2010; Wahner-Roedler *et al*., 2014). These findings suggest that grape seed extracts may have potential anticancer properties, warranting further investigation in human clinical trials.

The VITAL study, a prospective cohort study, investigated the association between dietary supplement use and cancer risk. The study enrolled 35,239 men aged 50 to 76 years, excluding those with a history of prostate cancer or high-grade prostatic intraepithelial neoplasia. Participants completed a questionnaire on supplement use (past ten years and current use) at baseline, with a median follow-up of approximately six years. The study found that grape seed supplement use was associated with a reduced risk of prostate cancer, specifically low-grade prostate cancer. Additionally, a non-significant risk reduction was observed for CRC (hazard ratio 0.72, 95% CI: 0.44-1.18), and no association was found with lung cancer risk (hazard ratio 0.97, 95% CI: 0.68-1.38) (Brasky *et al*., 2011). These findings suggest that grape seed supplement use may have a potential protective effect on prostate cancer development and possibly other cancers, although further investigation is needed to confirm these associations.

Wahner-Roedler *et al.* (2014) conducted a randomised, dose-escalation study to investigate the effects of grape seed extract on breast cancer prevention. Forty-six women were randomly assigned to receive one of four doses of grape seed extract (200, 400, 600, or 800 mg) daily for 12 weeks. Of these, 39 (84.8%) completed the study. The results showed that grape seed extract supplementation significantly decreased plasma oestrogens, including oestrone, oestradiol and oestrone sulphate. Notably, grape seed extract did not increase precursors of androgens, such as testosterone and androstenedione. These findings suggest that grape seed extract may have a potential role in breast cancer prevention by decreasing oestrogen levels, warranting further investigation in larger, long-term studies.

4.2.2.2 Proposed pharmacokinetics of grape seed extracts

To better understand the pharmacokinetics of grape seed extract, Sano *et al.* (2003) conducted a human trial that demonstrated the absorption of procyanidins after administering 2.0 g of grape seed extract, with procyanidin B1 detected in serum levels within 2 hours. Preclinical studies (*in vitro*) have shown that proanthocyanidins and procyanidins in grape seed extract inhibit ATP-binding cassette transporters and CYP3A4-mediated metabolism, potentially affecting the pharmacokinetics of anticancer

drugs (Mooiman *et al.,* 2014; Darweesh *et al.,* 2020). Grape seed extract has also been reported to inhibit CYP2D6, an isoenzyme involved in the biotransformation of tamoxifen's active metabolite, endoxifen (Goey *et al.,* 2013; Darweesh *et al.,* 2020). However, a clinical study with 30 healthy volunteers found that supplementation with 100 mg grape seed extract 2-3 times daily did not significantly affect CYP2D6 activity, suggesting safety when combined with substrates like tamoxifen (Goey *et al.*, 2013). In contrast, grape seed extract significantly decreased the metabolism of imatinib and its active metabolite in rats, suggesting a dose-dependent effect on pharmacokinetic pathways beyond CYP3A4 metabolism (Darweesh *et al.,* 2020). These findings highlight the potential of grape seed extract to interact with various pharmacokinetic pathways, warranting further investigation to fully understand its effects on drug metabolism and efficacy.

4.2.2.3 Preclinical and clinical trials as part of cancer intervention of grape seed extracts

Sharma *et al.* (2004) investigated the effects of grape seed extract as monotherapy and combination therapy on human breast carcinoma cell growth, including oestrogen-dependent (MCF-7) and oestrogen-independent (MDA-MB468 and MB231) cell lines. The study found synergistic effects of grape seed extract with doxorubicin, leading to cell growth inhibition and cell death, regardless of ER levels.

Vincent *et al.* (2013) highlighted the potential of antioxidants, such as Grape seed extract, to mitigate chemotherapy-induced toxicities, including cardiotoxicity, by reducing ROS. These adverse effects could be limited without affecting the cytotoxic effect. A systematic review by Olaku *et al.* (2015) examined preclinical studies (*in vivo* and *in vitro*) on the role of grape seed extract in preventing and treating chemo-/radiotherapy-induced toxicity. Of 41 studies, 40 showed positive outcomes when grape seed extract or grape seed proanthocyanidins were combined with chemo-/radiotherapy. The review highlighted the potential of grape seed extract to ameliorate toxicities associated with various chemotherapeutics, including doxorubicin and cisplatin. Currently, a phase 2, open-label, interventional study (NCT03087903) is recruiting participants to investigate Grape seed extract's effects on solid tumours and prostate cancer. This ongoing research aims to

further elucidate grape seed extract's potential in cancer management (National Library of Medicine, 2024).

4.3 Herbs, herbal extracts and herbal teas

4.3.1 Rooibos tea (*Aspalathus linearis*)

Rooibos tea (*Aspalathus linearis)(Fabaceae)* use has increased due to its important antioxidant activity (van Wyk, 2011). Herbal teas are rich in polyphenols and flavonoids; these are the main active components in herbal teas (van Wyk, 2011; Liu *et al.,* 2023). The phenolic metabolites are present in the fruits, leaves, roots and skin of the plant. In rooibos tea, a large amount of the flavonoid dihydrochalcone aspalathin is found; chalcone aspalathin is the main phenolic compound used for quality control (van Wyk, 2011; Liu *et al.,* 2023).

4.3.1.1 Form, consumption and safety data of Aspalathus linearis

This natural plants' twigs and leaves are used as a tea (Van Wyk & Gorelik, 2017). Fermented teas such as rooibos involve multiple methods, including picking, drying, rolling, further drying, screening and baking. The main component of fermented tea is catechin, which is oxidised during the fermentation process. Non-fermented tea is made from plant materials that are heated immediately after harvest, wound, compressed and dried to ensure the colour and ingredients are preserved (Liu *et al.,* 2023).

4.3.1.2 Effect of Aspalathus linearis on drug metabolism

To understand the pharmacological effect of the continuous intake of rooibos tea on the CYP3A enzyme, research was conducted in rats. Post intragastric administration of midazolam after two weeks of tea intake, a 60% decrease in levels of midazolam was found due to a 50% induction of CYP3A in the tea-treated group. This could lead to CYP3A4-mediated interactions between tea and various drugs (Matsuda *et al.,* 2007). Escudero-Vilaplana *et al.* (2023) identified possible drug interactions with antineoplastic agents when using an *in silico* analysis (Lexicomp® program, the About Herbs® database and a summary of product characteristics). For carboplatin, cisplatin, oxaliplatin and paclitaxel, possible interactions recognised were based on the effect rooibos tea exerts

as an anti-oxidant on free radicals, which compromise the antineoplastic therapy efficacy. The level of data used in the identification was rated as poor. Agents such as cyclophosphamide, docetaxel, doxorubicin, imatinib, irinotecan, tamoxifen and trastuzumab interactions were based on the increase in drug metabolism by CYP3A4, leading to decreased drug activity. This level of evidence was rated as fair.

4.3.1.3 Pre-clinical and clinical research on Aspalathus linearis

Protection against oxidative damage and its pro-oxidative activity are reported attributes of polyphenols in “unfermented” or green rooibos (von Gadow *et al.,*1997; Snijman *et al.,* 2009). Rooibos has been shown to have an effect on various mechanisms such as cellular proliferation, differentiation, angiogenesis, metastasis and apoptosis in both *in vivo* and *in vitr*o research (Samodien *et al.,* 2021).

Due to the growing popularity of *Aspalathus linearis,* Bond and Derbyshire (2020) presented evidence from human and laboratory studies in a systematic review. Table 4.1 provides an overview of studies in healthy volunteers evaluating the bioavailability and the effect of *Aspalathus linearis on* rehydration effectiveness. Table 4.2 provides an overview of the preclinical studies of *Aspalathus linearis* and the effect on oxidative stress based on antioxidant activity and chemo-protection.

Table 4.1 *Aspalathus linearis,* an overview of human studies in the last decade

Evidence in Human Trials					
Study (Author-Year-Location	**Subjects (Age, Gender-Number)**	**Study Design**	**Tea Intervention**	**Tea Intervention (Dosage)**	**Main Study Findings**
(Breiter *et al.*, 2011) Germany	n=12 healthy males	24-hr crossover trial.	Multiple rooibos mixtures: unfermented rooibos or placebo	10 g rooibos extracted with 500 ml boiling water seeped for 10 minutes	Average total of 0.76 nmol of flavonoids detected during the peak concentration, post intake of the rooibos tea- accounting for 0.26% compared to the total amount of flavonoids ingested.
(Utter *et al.,* 2010) USA	n=23 athletes	Randomised-cross-over design- three study arms.	Rooibos tea-carbohydrate beverage compared to bottled water (placebo)	Amount of rooibos tea not reported	The effect of rooibos tea in promoting rehydration was the same as plain water.
(Stalmach et al., 2009). Italy	n=10 volunteers	Bioavailability	Fermented or unfermented Rooibos tea	500 ml	The overall metabolite levels excreted were 82 and 352 nmol- accounting for 0.09 and 0.22% of the flavonoids in the fermented and unfermented drinks- respectively. Most of the aspalathin metabolites were excreted within 5 h of tea consumption- implying absorption in the small intestine.

Source: Adapted from (Bond & Derbyshire, 2020)

Table 4.2 *Aspalathus linearis,* an overview of laboratory studies in the last decade

Evidence from Laboratory Studies				
Study (Author-Year)	**Laboratory/ Mechanistic study**	**Rooibos Tea Intervention (type)**	**Main Outcomes**	**Main Findings**
(Lawal *et al*., 2019	*In vitro* antioxidant capacity	Aqueous extracts of fermented rooibos- green rooibos and honey bush	Oxidative stress	Herbal extracts offered protection against diesel exhaust particles that induced oxidative stress and inflammatory response.
(van der Merwe *et al*., 2015)	Male Fischer rats	Aspalathin-enriched green	Antioxidant activity	Glutathione reductase activity significantly ($p<0.05$) increased after 28 days- while glutathione content decreased after 90 days- suggesting an altered glutathione redox cycle.
(Waisundara & Hoon, 2015)	*In vitro* models of diabetes and cancer	Rooibos tea	Oxidative stress- diabetes- cancer	The rooibos tea extract was observed to have increased the enzymatic activity of catalase and superoxide dismutase activities in two *in vitro* disease models.
(Canda *et al.,* 2014)	n=40 male Wistar rats	Fermented rooibos unfermented rooibos a rooibos-derived commercial supplement or water.	Oxidative stress- Antioxidant activity	Fermented Rooibos led to a decrease ($p< 0.05$) in superoxide dismutase activity (SOD).
(Hong *et al.,* 2014)	Laboratory model	Rooibos tea	Oxidative stress	Rooibos tea appears to: (i) reverse the increase in stress-related metabolites (ii) prevent lipid peroxidation- (iii) restore stress-induced protein degradation- (iv) regulate glutathione metabolism and (v) modulate changes in the activities of antioxidant enzymes.

Study (Author-Year)	Laboratory/ Mechanistic study	Rooibos Tea Intervention (type)	Main Outcomes	Main Findings
(Baba *et al.,* 2009)	Wistar rats	Rooibos tea and water.	Oxidative stress-Antioxidant activity	Serum SOD levels were significantly higher in the rooibos group compared to the controls ($p< 0.05$).
(Marnewick *et al.,* 2009).	Rat liver	Unfermented and fermented rooibos	Chemo-protection	Unfermented rooibos significantly ($p<0.05$) to marginally ($p<0.1$) reduced the total number of foci (>10 microm). Fermentation seems to reduce the protective effect of herbal teas.
(Lee *et al*., 2004)	DNA strand scission	Rooibos tea	Antioxidant activity	Result suggests that total soluble phenolics (especially flavonoid) of rooibos tea are responsible for several antioxidant activities and preventive activity on peroxyl radical induced DNA strand scission.

Source: Adapted from (Bond & Derbyshire 2020) * Superoxide dismutase activity (SOD)

For *Aspalathus linearis*, evidence suggests any anticancer or anti-oxidant activity is limited to preclinical data and warrants further research (Bond & Derbyshire 2020).

4.3.2 Ginger (*Zingiber officinale Roscoe*)

The Zingiberaceae family encompasses approximately 1300 species, with *Zingiber officinale Roscoe*, commonly known as ginger, being a prominent member (Low Dog*,* 2010). Ginger is cultivated in subtropical regions, including Jamaica, India, Africa, and China. The rhizome of *Z. officinale* contains bioactive compounds, with 6-gingerol being the most abundant in fresh rhizomes and 6-shogaol predominating in dried, processed roots (Low Dog*,* 2010; Ozkur *et al.*, 2022). Notably, 6-shogaol has been shown to inhibit 5-hydroxytryptamine-3 (5-HT3), a serotonin receptor subtype, suggesting potential pharmacological activities (Low Dog*,* 2010; Ozkur *et al.*, 2022) and have shown beneficial biological anticancer effects (Kim *et al.,* 2014).

4.3.2.1 Formulation and dose

The optimal dosage of *Zingiber officinale Roscoe* varies depending on the specific product and concentration, “fresh or dried rhizome 1-4 g daily, fluid extracts (1:1 g/ml): 0.25-1 ml, three times daily (t.i.d.), tincture (1:5): 1.25-5 ml, three times daily (t.i.d.)” *(*Low Dog, 2010, p325).

4.3.2.2 Evidence of antioxidant activity of Zingiber officinale Roscoe

Danwilai *et al.* (2017) conducted a clinical trial to evaluate the antioxidant effects and safety of ginger extract in 43 patients undergoing chemotherapy. No unacceptable toxicities were reported. Antioxidant assays showed a significant increase in antioxidant activity and a decrease in oxidative stress in the ginger extract group receiving 6-gingerol 5mg (1.4% w/w of ginger extract with diluents) daily. Confirmation of ginger's scavenging effect on superoxide radicals and lipid peroxidation was reported; however, the study did not assess potential interactions between chemotherapy and ginger supplementation.

4.3.2.3 Evidence of anticancer properties of Zingiber officinale Roscoe

Ginger has demonstrated anticancer activity in various cancer cell lines, including colorectal and breast cancer (Ozkur *et al.*, 2022). A systematic review by Nachvak *et al.* (2023) analysed *in vitro* studies on ginger's anti-CRC properties, focusing on apoptosis pathways. The review found that ginger and its derivatives increase B-cell lymphoma-2-associated X (BAX), leading to cell death, decreasing BCL-2, inhibiting cell proliferation, enhancing caspase activity and promoting apoptosis. In breast cancer, 10-gingerol has been shown to prevent metastasis in Triple Negative Breast Cancer and reduce proliferation in certain breast cancer cell lines by upregulating BAX and downregulating BCL-2 (Kim *et al.*, 2022). Limited biomarker analysis from randomised clinical trials suggests that ginger supplementation (2 g/day) may reduce human telomerase reverse transcription in CRC or high-risk patients but does not significantly affect BCL-2 and BAX expression (Nachvak *et al.*, 2023). Preclinical studies have also demonstrated that combining ginger extract with chemotherapeutic agents like doxorubicin improves

treatment outcomes in murine breast cancer models, enhancing survival rates, reducing tumour mass, and promoting apoptosis (Ozkur *et al.,* 2022)

4.3.2.4 Proposed pharmacokinetic properties of Zingiber officinale Roscoe

In a study of 27 healthy volunteers, orally administered 6-, 8- and 10-gingerol plus 6-shogaol together with their conjugates at multiple doses of ginger extract standardised to 5% gingerols, 100, 250, 500, 100, 1500 and 2000 mg were given daily to determine the pharmacokinetic profile thereof (Low Dog, 2010). According to the findings, the constituents of ginger root are absorbed rapidly and detected as glucuronide metabolites in serum. Concentrations of ginger root (0.5%-2.5%) are only detectable in serum at a starting dose of 1 g, with the exception 6-gingerol, which is detectable at 250 mg. Ginger conjugate's T_{max} is around 45-120 minutes post oral administration, and the elimination half-lives range from 75-120 minutes at the 2 g dose (Low Dog, 2010). Containing more than 400 bioactive components, ginger has demonstrated inhibition of CYP enzymes and phosphorylated-glycoprotein transporters in human subjects, leading to the accumulation of crizotinib and consequently inducing hepatotoxicity (Cheng *et al.,* 2023).

4.3.2.5 Evidence on the clinical efficacy of Zingiber officinale Roscoe on chemotherapy-induced side effects

Chemotherapy-induced nausea and vomiting are a result of free radical production, leading to the stimulation of enterochromaffin cells in the gastrointestinal tract post-chemotherapy administration, which leads to the release of serotonin. This binding of serotonin to 5-hydroxytryptamine-3 receptors on intestinal vagal afferent nerves triggers the vomiting reflex (Rapoport, 2017). This is classified into five categories: acute, delayed, anticipatory, breakthrough, and refractory. Acute chemotherapy-induced nausea and vomiting arise within 24 hours after chemotherapy administration, whereas anticipatory chemotherapy-induced nausea and vomiting is deemed a "general" response to chemotherapy. Despite the use of the recommended standard prophylaxis, breakthrough nausea and vomiting occur within five days post-chemotherapy administration and refractory nausea and vomiting only occur in subsequent chemotherapy cycles post the occurrence of breakthrough chemotherapy-induced nausea and vomiting in previous

cycles. Despite standard prophylaxis, breakthrough nausea and vomiting can occur, and refractory nausea and vomiting may emerge in subsequent chemotherapy cycles (Wood *et al.,* 2018).

To enhance the quality of life and clinical outcomes for cancer patients, a holistic approach combining conventional treatments with integrative therapies is recommended (Malossiotis *et al.*, 2024). However, the evidence for using ginger to control chemotherapy-induced nausea and vomiting is limited, leading to varying conclusions from reputable organisations. The SIO recommends ginger use based on low-level evidence and the American Society of Clinical Oncology cannot advise for or against ginger use due to insufficient evidence. The Multinational Association of Supportive Care in Cancer and the European Society for Medical Oncology cannot recommend ginger as adjuvant treatment due to conflicting data, heterogeneous dosages, and non-guideline recommended antiemetic use in clinical trials (Malossiotis *et al.,* 2024).

4.3.2.6 Adverse effects and risks related to Zingiber officinale Roscoe when used with chemotherapy

A systematic review of 17 randomised studies, including non-cancer research, deemed ginger relatively safe, with the most common adverse effects being gastrointestinal (GI) symptoms such as reflux, diarrhoea, bloating and epigastric distress (Ahn *et al.,* 2020). Ginger's antioxidant and anticancer properties, as well as its potential in managing chemotherapy-induced nausea and vomiting, have been documented. However, due to conflicting results, dosage variability among studies, risk of bias and limited information on chemotherapy interactions, it remains unclear whether ginger is safe to use as adjuvant treatment in cancer patients (Ahn *et al.*, 2020).

4.4 Medicinal plants and medicinal plant extracts or seeds

4.4.1 Cannabis and cannabinoid-based medicine

Cannabis, a flowering plant with a centuries-long history of medicinal and recreational use, has garnered significant scientific attention for its therapeutic potential (Turgeman & Bar-Sela, 2019). Substantial evidence has led to the approval of medicinal cannabis and

cannabinoid-based medicines in several countries, particularly in the context of chemotherapy-induced nausea and vomiting and cancer-related pain management (Turgeman & Bar-Sela, 2019). The biological activity of cannabis is attributed to its constituent cannabinoids, which vary in qualitative and quantitative composition across different plant varieties. The highest cannabinoid content is found in the resin and glandular trichomes of female flowering tops (Woerdenbag *et al.,* 2023). Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most extensively investigated cannabinoids (Legare *et al.,* 2022). These compounds have been shown to interact with the body's endocannabinoid system, modulating various physiological processes (Woerdenbag *et al.,* 2023). The medicinal cannabis interventions include single-molecule analogues of THC, pharmaceutical cannabis-based combinations of THC and CBD and non-pharmaceutical cannabis-based medicines reported as ‘hemp oil’ and inhaled cannabis sourced from the Cannabis sp. plant (Legare *et al.,* 2022).

4.4.1.1 Pharmacokinetics of cannabis or cannabinoid-based medicine

The pharmacokinetics of cannabis administration vary depending on the route of administration, with different absorption properties and bioavailability of THC and CBD (Legare *et al.,* 2022). Traditional routes include pulmonary (smoking) and oral routes, while alternative routes include oral-mucosal and sublingual administration (Woerdenbag *et al.,* 2023). Smoking cannabis results in rapid absorption and maximal plasma concentrations within 10 minutes, while oral administration leads to slower absorption and maximal concentrations after several hours. Sublingual administration of cannabis oil shows similar bioavailability to oral administration. THC and CBD are highly bound to plasma proteins and rapidly distribute to well-vascularized organs and fat tissue, prolonging the elimination half-life (Woerdenbag et al., 2023). Metabolism occurs in the liver through cytochrome P450 isoenzymes (CYP3A4, CYP2C9, and CYP2C19 for THC, and CYP3A4 and CYP2C19 for CBD) and glucuronidation by UDP-glucuronosyltransferases (UGTs). The elimination half-life of THC and CBD varies among users. CBD may interact with THC's bioavailability and metabolism, potentially inhibiting cytochrome P450 and increasing THC's effects, as seen in a recent clinical trial where

high-dose CBD increased THC's impairment of cognitive and psychomotor activity and heart rate (Woerdenbag *et al.,* 2023).

4.4.1.2 Formulation, extracts and consumption of cannabis or cannabinoid-based products

Cannabinoids are classified based on their source of production, with three categories: synthetic cannabinoids (manufactured from classical and non-classical agents structurally similar to endocannabinoids), phytocannabinoids (naturally occurring in the Cannabis plant), and endocannabinoids (endogenously produced by humans and mammals) (Turgeman & Bar-Sela, 2019). The Cannabis plant has three identified species: *Cannabis sativa, Cannabis indica*, and *Cannabis ruderalis* (Turgeman & Bar-Sela, 2019). The medicinal plant can be administered in its herbal form (naturally extracted plant) or synthetic manufactured form, with various routes of administration contributing to its pharmacokinetic profile (Legare *et al.,* 2022). Oral consumption methods include tablets, oils, edibles, oromucosal, and sublingual forms, while alternative routes include transcutaneous, inhalation, injection, rectal and more (Häuser *et al.,* 2023). However, orally administered cannabinoids are subject to extensive first-pass metabolism in the liver (approaching 95%), highlighting the need for alternative routes of administration to optimise bioavailability and therapeutic efficacy (Legare *et al.,* 2022).

4.4.1.3 Evidence of anti-cancer properties of Cannabis or cannabinoid-based products

Preclinical studies have demonstrated the potential anticancer properties of medicinal cannabis, particularly in modulating key survival and immunomodulatory factors (Brown *et al.,* 2019). Cannabinoids, such as CBD and THC, have shown promise in enhancing the efficacy of first-line treatments in oncology. These findings suggest that cannabinoids may inhibit tumour growth and proliferation, induce apoptosis and autophagy, inhibit angiogenesis, migration, invasion, and metastasis, enhance the effects of antineoplastic agents, such as temozolomide and radiation and act synergistically with chemotherapeutic agents, such as docetaxel and paclitaxel (Woerdenbag *et al.,* 2023).

A phase 1b trial investigated the efficacy and safety of oromucosal nabiximols spray, containing synthetic THC and CBD, in combination with dose-intense temozolomide in glioblastoma patients (Twelves *et al.,* 2021). Although the sample size was small, the results showed promising overall survival rates at one year, with 83% in the nabiximols-treated group compared to 44% in the placebo-treated group. Additionally, the study found that nabiximols reduced chemotherapy-related adverse events such as vomiting, dizziness, fatigue, nausea, and headache. No interactions were observed between nabiximols and temozolomide, indicating the safe use of cannabinoids during regular cancer therapy. These findings warrant further investigation in an upcoming phase 2 trial to fully assess the efficacy of cannabinoids in glioblastoma treatment.

Another phase 2 randomised controlled trial conducted in New Zealand investigated the safety and efficacy of THC-containing medicinal cannabis in patients with high-grade glioma (Schloss *et al.,* 2021). The study found that a single nightly dose of THC was well-tolerated, with no serious adverse effects, and improved sleep, functional well-being, and quality of life. Notably, a significant tumour reduction was observed in 9% (8/88) of patients at 12 weeks, suggesting a potential anti-tumour effect when combined with standard treatment and THC/CBD oil.

4.4.1.4 Management of chemotherapy-induced adverse effects

Evidence supports regulatory approval of cannabis in the management of chronic pain and chemotherapy-induced adverse effects (Turgeman & Bar-Sela, 2019). Clinical trials have focussed on cannabis for the management of cancer therapy-associated adverse effects. This includes chemotherapy-induced nausea and vomiting, cachexia and pain management (Brown *et al.,* 2019).

4.4.1.5 Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

The endocannabinoid system, comprising CB1 and CB2 receptors, plays a crucial role in regulating various physiological processes, including nausea and vomiting (Legare *et al.,* 2022). Endocannabinoids, such as anandamide and 2-arachidonoylglycerol, bind to

these receptors as full or partial agonists. THC, the primary psychoactive constituent of cannabis, exhibits agonist activity at both CB1 and CB2 receptors, with a higher affinity for CB1. In contrast, CBD acts as an antagonist at CB1 and an inverse agonist at CB2. The antiemetic properties of THC are believed to be mediated by stimulation of the CB1 receptor, as blocking these receptors leads to vomiting (Woerdenbag *et al.,* 2023).

A Cochrane review by Smith *et al.* (2015) evaluated the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer. The review included 23 randomised clinical trials, mostly crossover designs, conducted between 1975 and 1991. The results showed that compared to placebo, cannabinoids were associated with a higher chance of complete absence of vomiting and nausea. Cannabinoids had a higher risk of adverse events, such as feeling high, dizziness, dysphoria, euphoria, sedation, and withdrawal due to adverse events. There was no significant difference between cannabinoids and prochlorperazine in terms of nausea and vomiting outcomes, and participants preferred cannabinoids to placebo and prochlorperazine. The quality of evidence was generally low to moderate, and the trials were at risk of bias due to design limitations and outdated chemotherapy regimens. The review concluded that cannabis-based medications may be useful for refractory chemotherapy-induced nausea and vomiting, but the methodological limitations of the trials limit the confidence in the results.

A recent multi-centre, randomised, placebo-controlled trial (PhII/III) investigated the efficacy of adding oral THC/CBD cannabis extract to guideline-consistent antiemetic prophylaxis in adults experiencing chemotherapy-induced nausea and vomiting during moderate and highly emetogenic intravenous chemotherapy regimens. The study aimed to determine the difference in complete response (no emesis and no rescue medications) between THC/CBD and placebo groups. The results showed a significant increase in complete response with THC/CBD (24%) compared to placebo (8%), with an absolute difference of 16% (P-value 0.01). Early termination was due to slow recruitment; however, findings still suggest that oral THC/CBD is a well-tolerated and effective treatment for chemotherapy-induced nausea and vomiting, improving patient outcomes. The most

common regimens were doxorubicin/cyclophosphamide (31%) and fluorouracil/oxaliplatin (FOLFOX, 17%), 97% received corticosteroid & 5-HT3 antagonist, 80% received NK-1 antagonist, and 10% received olanzapine. Future analyses will focus on quality of life and cost-effectiveness (Mersiades *et al.,* 2023). Conclusive evidence on THC efficacy in chemotherapy-induced nausea and vomiting was also reported by Jugl *et al*. (2020), who did a systematic review of the evidence for cannabis and cannabinoids as adjuvant therapy in palliative and supportive oncology care.

4.4.1.6 Cannabis-based medicines and medical cannabis for adults with cancer pain

Another Cochrane review conducted by Häuser *et al.* (2023) evaluated the efficacy and safety of cannabis-based medicines for cancer-related pain management in adults. The review included 14 studies with 1823 participants, comparing cannabis-based medicines to placebo or registered analgesics. The studies assessed various cannabis-based medicines, including nabiximols (THC and CBD) and synthetic THC analogues, in different settings and cancer types. The review found no clinically relevant benefit in pain reduction or Patient Global Impression of Change, no difference in withdrawals due to adverse events or serious adverse events, and no difference in mean pain intensity reduction when used as an add-on treatment for opioid-refractory cancer pain. Low-certainty evidence for synthetic THC analogues showing superiority to placebo but not to low-dose codeine in reducing cancer pain and no added value of CBD oil in reducing pain intensity in advanced cancer patients. These results did not include studies using herbal cannabis.

4.4.1.7 Adverse effects and safety of cannabis products

Cannabis and its products have demonstrated a favourable safety profile with limited adverse effects (Woerdenbag *et al.,* 2023). A prospective one-year study in non-cancer-related pain patients and a phase I randomised trial in healthy volunteers showed that cannabis was well-tolerated, with mild and moderate adverse effects, including diarrhoea, nausea, headache and somnolence. A retrospective Canadian study with 9766 adults using cannabis products reported dry mouth, drowsiness and dizziness as common adverse effects, with CBD-containing oils being the most frequently used products. A

large Israeli prospective study with approximately 10,000 patients using medicinal cannabis showed a low incidence of serious adverse effects (Woerdenbag *et al.,* 2023). Pharmacovigilance of cannabis products is still limited, as cannabis use has been largely recreational. Cannabis, THC and euphorigenic cannabinoids continuous exposure should also be monitored as it has been linked to the induction of psychotic symptoms in a significant proportion (20-50%) of individuals (Legare *et al.,* 2022). Symptoms can manifest as both positive and negative and typically resolve after the intoxication period; alternatively, it can lead to cannabis-induced acute persistent psychosis. Additionally, a significant relationship has been found between cannabis use and exacerbated mania symptoms in patients with bipolar disorder, as well as a 3-fold increase in mania symptoms in nonclinical patients (Legare *et al.,* 2022). As the legalisation of cannabis products becomes clearer and more nuanced in many countries, the monitoring, detection, assessment and management of adverse reactions associated with medicinal cannabis will develop further.

Concomitant use of cannabis and immunotherapy in cancer treatment revealed potential concerns (Bar-Sela *et al*., 2020). Cannabis, with its immunomodulatory effects, may interact with ICIs, impacting treatment outcomes. Cannabis consumption during ICI immunotherapy was associated with decreased time to tumour progression and overall survival, suggesting a potential negative impact on cancer treatment efficacy (Bar-Sela *et al.,* 2020).

4.4.2 Cancer Bush (*Sutherlandia frutescens*)

Sutherlandia frutescens, commonly known as Cancer Bush or "musa-pelo" in Sesotho, is a traditional medicine in South Africa used to treat various diseases (Moteetee & van Wyk, 2007; van Wyk & Albrecht, 2008). Commercialisation has made available various forms of the plant, including dried leaves, teas, extracts, ointments and tablets made from powdered herbs (van Wyk, 2011). The plant contains diverse chemical compounds, including pinitol with insulin-like effects, triterpenoid saponins, at least six flavonoids and high levels of free and protein-bound amino acids (van Wyk & Albrecht, 2008).

4.4.2.1 Formulation and administration of Sutherlandia frutescens

The ingestion of dried and ground *Sutherlandia* leaves enables the complete bioavailability of its constituents (Fasinu *et al.,* 2013). Commercial capsules contain 300 mg of dried leaves, recommended for twice-daily administration. Traditionally, the average consumption is 2.5-5 g of dry material or decoctions, with a reported maximum intake of 5 g of leaves, stems, and pods twice daily without observed toxicity or harm. Additionally, teas made from the leaves are a popular form of consumption (van Wyk & Albrecht, 2008).

4.4.2.2 Preclinical evidence on anticancer properties of Sutherlandia frutescens

Preclinical studies have demonstrated the potential anticancer properties of *Sutherlandia* extracts in various cancer cell lines. Research has shown that *Sutherlandia* extracts inhibit the growth of hormone receptor-positive, oestrogen-dependent cell lines (Steenkamp & Gouws, 2006), induce cytotoxicity in cervical carcinoma cells (Chinkwo, 2005), induce apoptosis and downregulate the phosphoinositide 3-kinase pathway in colon cancer cells (Leisching *et al.,* 2015). Inhibition of the proliferation of both MCF-7 and MDA-MB-468 in human breast cells has been documented when using the commercially available formulations (Steenkamp & Gouws, 2006). D-pinitol, a constituent of *Sutherlandia frutescens,* has also been shown to attenuate cisplatin-induced nephrotoxicity in mice, showing potential renal protective effects (Vaisakar *et al.*, 2018). Lin *et al.* (2016) also suggest that the *Sutherlandia frutescens* extract may exert an anti-cancer effect by targeting a specific pathway in prostate cancer cell lines of transgenic adenocarcinoma of the mouse prostate. These findings suggest that *Sutherlandia* extracts and their constituents may have antiproliferative and apoptotic effects, warranting further investigation into their potential as anticancer agents.

4.4.2.3 Safety of Sutherlandia frutescens in healthy adults

A phase 1 clinical trial assessed the tolerability of *Lessertia frutescens (Sutherlandia)* in 25 healthy adults (Johnson *et al.,* 2007). In this randomised, placebo-controlled design, 12 participants received 400 mg *Sutherlandia* leaf powder capsules (600 µg canavanine

per capsule) twice daily (800 mg/day) for three months, while the remaining participants received a placebo. The study evaluated adverse effects, physical and vital signs, blood indices, and biomarker levels. No significant differences in adverse effects between the active intervention and placebo groups were detected. Canavanine, (a *Sutherlandia* biomarker), levels were not detected, which could indicate limited absorption of *Sutherlandia*.

4.4.2.4 Proposed pharmacokinetic properties of Sutherlandia frutescens

Fasinu *et al.* (2013) investigated the effects of crude extracts of *Sutherlandia frutescens* on human liver microsomes. Results suggest concentration dependant inhibition of CYP1A2, CYP2A6, CYP2C8, CYP29C, CYP2C19 and CYP3A4/5, P-gp, OATP1B1, and OATP1B3. A dose of 300 mg yields a gastrointestinal concentration 50 times the IC_{50} value for most enzymes and transport proteins. Minocha and colleagues (2011) found the interactions between *Sutherlandia* extracts and antiretrovirals such as nevirapine and atazanavir. The long-term use of *Sutherlandia frutescens* extracts in rats significantly reduces the pharmacokinetic parameters of nevirapine. Chronic exposure leads to a decrease in the area under the curve and maximum C_{max} values up to 50%, $p<0.05$. The pre-clinical data on the co-administration of *Sutherlandia* with low-therapeutic-index molecules shows possible herb-drug interactions, leading to a reduction in the efficacy of these treatments (Minocha *et al.*, 2011).

4.5 Vitamins, minerals and dietary supplements

4.5.1 Multivitamins and vitamins or minerals use in cancer patients

Supplement use is common among cancer patients and cancer survivors (Velicer & Ulrich, 2008). Studies from multiple cancer sites reported usage of 64% to 81% for any vitamin or mineral and 26% to 77% for multivitamins among cancer survivors. Post-diagnosis, around 14% and 32% of survivors initiate supplement use. Breast cancer survivors are among the highest users, compared to prostate cancer survivors, reporting the lowest use. As many as 68% of physicians are not aware of the supplement use among their cancer patients (Velicer & Ulrich, 2008).

4.5.1.1 Post-diagnosis use of antioxidant vitamin supplements

A systematic review and meta-analysis of prospective cohort studies were conducted to examine post-diagnosis antioxidant vitamin supplement use and overall survival (Li *et al.,* 2021). The studies reported the use of multivitamins, including Vitamin C (ascorbic acid), Vitamin A or Vitamin E and certain minerals. Evidence from the Prospective cohort Diet, Exercise, Lifestyle and Cancer Prognosis (DelCaP) research shows no significant difference in overall survival. Four additional studies also examined post-diagnosis anti-oxidant vitamin supplements intake and breast cancer-specific survival; again, the hazard ratio was calculated and was not statistically significant. Total mortality and anti-oxidant vitamin supplement use during chemotherapy pooled data continued to show non-statistical significant outcomes, and therefore, in summary, the results of the meta-analysis done by Li *et al.* (2021) on an estimated 17 000 breast cancer patients concluded that overall survival did not worsen when using these supplements. When exploring results for Vitamin C supplementation alone, this was associated with better overall survival outcomes for patients.

4.5.2 Vitamin C (L-Ascorbic acid, ascorbate)

Ascorbic acid, a water-soluble micronutrient (Padayatty *et al.,* 2010), plays a vital role in various biological processes, including enzymatic reactions and antioxidant functions. Its significance in human health and disease prevention has been well established. Notably, the concept of utilising ascorbic acid as a cancer treatment was first proposed by Nobel laureates Linus Pauling and Ewan Cameron over five decades ago (Cameron & Pauling, 1976). Their pioneering work laid the foundation for subsequent research exploring the potential of ascorbic acid in cancer management, highlighting its promise as a complementary and alternative therapy. The scientific community continues to investigate ascorbic acid's anti-cancer properties, aiming to elucidate its mechanisms of action and optimise its therapeutic applications.

Humans, unlike animals, lack the ability to synthesise ascorbic acid endogenously, relying solely on dietary intake (Carr & Cook, 2018). Studies have consistently shown that cancer patients exhibit lower mean plasma ascorbic acid levels compared to healthy individuals,

with the severity of disease directly correlating with the prevalence and severity of hypovitaminosis C. *Ex vivo* analysis of CRC tumours revealed significantly lower ascorbic acid concentrations compared to normal tissue, with higher-grade tumours displaying proportionately lower ascorbic acid levels. This depletion may be attributed to enhanced metabolic turnover due to the oxidative and inflammatory burden of the disease process or chemotherapy, increasing ascorbic acid requirements in cancer patients. Notably, conventional anticancer therapies, including cisplatin, fluorouracil, nilotinib, and interleukin-2, have been shown to decrease ascorbic acid levels in oncology patients. The off-target oxidative stress generated by chemotherapeutic agents like cisplatin may contribute to ascorbic acid depletion. When used in combination with radiotherapy, the addition of high doses of ascorbic acid has been shown to act synergistically and increase tumoricidal effects. The need for more studies to determine the optimal timing and dosing of ascorbic acid during concurrent use with radiotherapy is required (Carr & Cook, 2018).

4.5.2.1 Evidence of anticancer properties of ascorbic acid

The proposed anticancer activities of ascorbic acid have been reported; commonly described is ascorbic acid's activity as a pro-oxidant (Böttger *et al.,* 2021). *In vitro* elicitation of hydrogen peroxide-dependent cytotoxicity within tumour cells with high dose ascorbic acid enables reduction of the transition of metal ions, which sequentially generates hydrogen peroxide. Little human evidence is available to confirm this pro-oxidant mechanism. Another reported mechanism is the overexpression of p53 when combination therapy of ascorbic acid and certain chemotherapies are used, again suggesting ascorbic acid-mediated cytotoxicity (Böttger *et al.,* 2021; Carr & Cook, 2018). Pre-clinical findings have described multiple mechanisms of actions of ascorbic acid in combination with cancer chemotherapy. A few anticancer activities include oxidative stress and DNA damage, decreasing antioxidant enzymes, mitochondrial stress, BCL-2 inhibition, p53 overexpression, adenosine triphosphate depletion, increasing iron, immunomodulation, increasing collagen and a-tubulin acetylation (Böttger *et al.,* 2021).

4.5.2.2 Formulation and administration of ascorbic acid

The utilisation of ascorbic acid among participants in this study varied from the recommended daily allowance (75 mg for females and 90 mg for male adults) to doses of up to 1000 mg daily (National Institute of Health, 2021). It is crucial to differentiate between orally administered ascorbic acid and pharmacologically high doses of intravenous (IV) ascorbic acid, which are required to achieve cytotoxic effects in cancer cells, as reported in preclinical research (Böttger *et al.,* 2021). In oncology settings, IV ascorbic acid administration at a dose of 4 g/kg has been investigated (Böttger *et al.,* 2021). As expected, the route of administration significantly influences peak plasma ascorbic acid concentrations, with IV administration resulting in a 70-fold greater concentration compared to oral administration. A systematic review by van Ghorkom *et al*. (2019) found that Phase II and III studies included in the review demonstrated a positive effect on survival time when ascorbic acid supplementation was administered IV, with or without oral supplementation.

4.5.2.3 Potential interactions or safety concerns

Concerns about the possible interactions between chemotherapeutic agents and ascorbic acid are ongoing (Carr & Cook, 2018). Due to the potent antioxidant activity of ascorbic acid, administration of ascorbic acid concurrently with cytotoxic agents is generally avoided. Considering the different mechanisms of action, not all chemotherapeutic agents act via oxidative mechanisms. This has led to recommendations around the administration of natural therapy to allow for five half-lives to elapse before the administration of chemotherapeutic agents. The half-life of Ascorbic acid is <2 hours in circulation based on its rapid renal clearance, allowing for IV ascorbic acid administration the day before or after chemotherapy. For chemotherapeutic agents with effects outside of oxidative mechanisms, concurrent administration can be possible. Human trials have shown no adverse effects when combining IV ascorbic acid with various chemotherapeutic agents like carboplatin, paclitaxel, decitabine, cytarabine, aclarubicin, gemcitabine, erlotinib, and temozolomide. In many cases, a decrease in off-target toxicity and an improvement in health-related quality of life were observed (Carr & Cook, 2018).

Clinical studies show ascorbic acid monotherapy to be tolerable up to 3 g/kg doses in various advanced cancers (Böttger *et al.,* 2021). Commonly reported adverse effects were hypokalaemia, hypernatremia, hypertension and anaemia. Other events of relevance include kidney stones in patients with renal dysfunction and thromboembolism, the latter attributed to cancer. A clinically significant anti-cancer effect was not seen in these studies (Böttger *et al.,* 2021). Similar safety findings were confirmed by van Ghorkom *et al.* (2019) systematic review.

4.5.2.4 Preclinical and clinical trials on ascorbic acid as part of cancer intervention

Wittes (1985) published in the New England Journal of Medicine contradictory results from preclinical and clinical studies regarding the role of ascorbic acid in cancer. The need for robust results to assist with clinical decision-making was lacking. Understanding the evolution of this topic based on newer clinical data is summarised below.

4.5.2.4.1 A meta-analysis of studies between ascorbic acid supplementation, dietary use and the association of breast cancer survival

Prospective observational studies published between 1993 and 2013 are used in this meta-analysis by Harris *et al.* (2014). Ascorbic acid supplementation, in particular, five studies examined post-diagnosis ascorbic acid use and mortality risk; six studies included breast cancer-specific mortality. The results confirm a statistically significant 19% reduced risk compared to no supplementation post-diagnosis with similar outcomes in breast cancer-specific mortality. Two studies reported the approximate dosages used as 400 mg or less in the Shanghai Breast Cancer Survival Study, while in the Swedish Mammography Cohort, the most frequent dose was estimated at 1000 mg. The limitations of these results include the lack of information regarding the use of chemotherapy or radiotherapy in combination with ascorbic acid. Data from the Life After Cancer Epidemiology study reveals contrary results with no clear benefit of ascorbic acid usage with chemotherapy or radiotherapy (Harris *et al.,* 2014).

4.5.2.4.2 Preclinical and clinical data on high-dose ascorbic acid as monotherapy

Promising anticancer effects in preclinical models within multiple cancer types have been reported (Böttger *et al.*, 2021). This includes leukaemia, colon cancer, melanoma, pancreatic cancer and prostate cancer, with similar results seen in lung cancer, breast cancer, ovarian cancer, hepatocellular carcinoma, thyroid cancer, neuroblastoma and more. Tumour growth inhibition of up to 40%-60% was noted with doses of ascorbate 1-4 g/kg administered intravenous or intraperitoneal daily to maintain ascorbic acid levels inside the tumour and reduce metastasis formation with 50 to 90% *in vivo*. The high dose was well tolerated with no increase in toxicity and simultaneously prevented other adjuvant treatment side effects. In conclusion, *in vitro* and *in vivo* studies have shown promising outcomes (Böttger *et al.,* 2021).

4.5.2.4.3 Preclinical and clinical data on high dose ascorbic acid as combination therapy.

A total of 71 studies identified in the preclinical setting for combination use of ascorbic acid investigated 59 combinations, this includes chemotherapeutic agents, radiotherapy and newer targeted therapies. The efficacy of ascorbic acid as a combination therapy reported synergistic effects with carboplatin, cisplatin, chlorambucil, 5-FU and gemcitabine by enhancing the efficacy of the chemotherapeutic agent in various cancer cell types (Böttger *et al.*, 2021). Contradictory studies have shown that ascorbic acid reduces the effect of doxorubicin, methotrexate and cisplatin (Unlu *et al.,* 2016). The addition of ascorbic acid during radiation or chemo-radiation of preclinical cancer models has shown it to act as a radiosensitiser. Combination use with targeted therapies includes kinase inhibitors, mitochondrial inhibitors, HER2 therapy and hormonal therapies, which continue to report a synergistic effect and emphasise the potential of adjuvant ascorbic acid therapy. Recent results also show a positive synergistic effect of ascorbic acid and checkpoint inhibitors or immunotherapy in mouse models (Böttger *et al.,* 2021).

Phase I and II studies analysing the use of ascorbic acid in combination with cancer chemotherapy, inclusive of radiation therapy, have been done. The majority of the studies

are dose escalation studies and show similar trends as the pre-clinical research towards positive disease control and objective response rates. Study limitations include a small number of participants and are underpowered to determine the efficacy of ascorbic acid (Böttger *et al.*, 2021).

Based on the positive findings in phase I and II studies, the VITALITY Study: A Randomised, Open-Label, Multicenter, Phase 3 Study of High-Dose Vitamin C Plus FOLFOX Bevacizumab versus FOLFOX Bevacizumab in unresectable, untreated metastatic colorectal cancer (mCRC) was conducted to compare the efficacy and safety of high-dose Vitamin C plus FOLFOX bevacizumab versus FOLFOX bevacizumab as first-line treatment in patients with mCRC. Wang *et al.* (2022) concluded that high-dose ascorbic acid (1.5 g/kg/day) in combination with chemotherapy failed to show superior progression-free survival compared with conventional chemotherapy in chemotherapy-naive patients with mCRC as first-line treatment but may be beneficial in patients with mCRC harbouring RAS mutation.

Currently, multiple ongoing studies in different stages of clinical development on ascorbic acid use in cancer are active on Clinical trials.gov. The research continues with ascorbic acid as monotherapy or combination therapy. Future results will support informed decision-making on this topic.

4.6 Other practices or compounds

4.6.1 Sodium bicarbonate

Sodium bicarbonate, commonly used as an antacid to treat gastric hyperacidity (Yang *et al.,* 2020), has potential applications in oncology. The tumour microenvironment in various cancers is characterised by an acidic extracellular pH, driven by the accumulation of metabolic by-products such as H^+ ions, lactate, and CO_2 (Yang *et al.,* 2020). This acidic environment supports cancer cell survival, migration and metastasis and may contribute to chemotherapeutic resistance (da Silva *et al.*, 2018). Targeting tumour acidity through neutralisation and increasing tumour pH may be a promising strategy to impact cancer cell progression (Yang *et al.,* 2020). Modulating the tumour microenvironment pH may enhance the efficacy of cancer therapies and improve treatment outcomes.

4.6.1.1 Evidence on the anticancer activity of sodium bicarbonate

Sodium bicarbonate used as monotherapy in mice demonstrated some effect in cancer cell lines such as breast- MDA-MB-231 and prostate cancer PC3 cell line compared to aggressive phenotypes B16 melanoma and Panc02 pancreatic cancer (Yang *et al.,* 2020). Therefore, combination use with anticancer treatment as adjuvant therapy was further investigated. Early research on mice with MCF-7 human breast cancer xenografts treated with bicarbonate-supplemented water in combination with doxorubicin showed a two- to three-fold increase in the effect of doxorubicin. The elevation of uptake of weak-base chemotherapeutic molecules could be enhanced by extracellular alkalisation. Conversely, the effect could be diminished when used in combination with weak acidic chemotherapeutics (Yang *et al.,* 2020). Delayed tumour growth and an increase in tumour necrosis were seen in different tumour types when used in combination with other cancer therapies, as seen in Table 4.3.

Table 4.3 *In vivo* research of combination sodium bicarbonate with anticancer therapies

Anticancer Therapy	Tumour Type	Animal Models	Sodium Bicarbonate	Outcomes
Chemotherapy				
Doxorubicin 2 mg/kg intraperitoneal (ip)	Breast cancer	MCF-7 xenograft	200 mM po as required	Increased therapeutic efficacy
Mitoxantrone 12 mg/kg) IV	Breast cancer	C3H allograft	0.7 ml intramuscular $NAHCO_3$	3 fold increase of therapeutic index
VEGFR2 Inhibitor				
Sunitinib 40 mg/kg orally (po)	CRC	HT29 xenograft	200 mM po as required	Delayed tumour growth, decrease in blood vessels, increases tumour necrosis, decrease in expression of VEGFR2, delayed tumour growth MC-38 allograft
Rapamycin 3 mg/kg ip	CRC	HT29 xenograft	200 mM po as required	Delayed tumour growth, increased tumour necrotic surface increased MC-38 allograft
ICI				
Anti-programmed cell death protein-1 (Anti-PD-1) therapy	Melanoma	B16 allograft	200 mM po as required	Modest effect on tumour growth ($P<0.05$)
Anti-PD-1 therapy	Pancreatic cancer	Panc02 allograft	200 mM po as required	Tumour growth delayed ($P< 0.005$)
Anti-cytotoxic T-lymphocyte-associated protein 4 (Anti-CTLA4) therapy	Melanoma	B16 allograft	200 mM po as required	No effect on tumour growth ($P=0.54$)
Anti-PD-1 therapy/Anti-CTLA4 therapy	Melanoma	B16 allograft	200 mM po as required	No effect on tumour growth
Adoptive T-cell therapy	Melanoma	B16 allograft	200 mM po as required	No effect on tumour growth. Long term (120 day) survival rate (40% vs 10%) T-cell persistence increase

Source: (Yang *et al.,* 2020, p3)

CRC: Colorectal cancer; ICIs: Immune checkpoint inhibitors; VEGFR: Vascular endothelial growth factor receptor

An early phase I, randomised, controlled, interventional study of systemic chemotherapy in combination with sodium bicarbonate for unresectable gastric cancer was registered on Clinical Trials.gov. The current status on the website is listed as “unknown”, and no

results have been published to date. NCT03910140, another study to support previously published preclinical data and validate tumour response rate using trans-arterial chemoembolisation and adding a solution of sodium bicarbonate to the cytotoxic drugs described for targeting intra-tumour lactic acidosis, is within its completion timeframe. This prospective non-controlled single-arm study of targeting intra-tumour lactic acidosis, trans-arterial chemo-embolism treatment of 5% sodium bicarbonate infused alternatively with doxorubicin-lipiodol emulsion for hepatocellular carcinoma should have published results in the near future (National Library of Medicine, 2019).

4.6.1.2 Management of oral mucositis with sodium bicarbonate in cancer patients

Oral mucositis is a common side effect of anticancer chemotherapy and head and neck radiotherapy, affecting approximately 90% of patients (Di Fede *et al.,* 2023). Inflammation response of epithelial mucosa to chemo-radiotherapy cytotoxic effects leads to mucositis, a painful side effect of antineoplastic treatments. The epithelial mucosa's inflammatory response to the cytotoxic effects of chemo-radiotherapy leads to mucositis, a painful and debilitating side effect of antineoplastic treatments. Mucositis is characterised by damage to the mucosal lining, resulting in ulceration, erosion, and discomfort (Pulito *et al.,* 2020). The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology recommends the use of bicarbonate of soda (sodium bicarbonate) mouthwash for oral mucositis management despite limited and conflicting evidence of its effectiveness. A recent systematic review by Di Fede *et al.* (2023) confirmed the use of sodium bicarbonate rinses for oral mucositis management despite the lack of robust evidence. However, non-selective use of bicarbonate of soda may lead to sudden pH increases, potentially delaying pharmacological interventions indicated for the management of oral mucositis (Di Fede *et al.,* 2023). Currently, clinical trials are recruiting to investigate the preventive effects of sodium bicarbonate on oral mucositis in head and neck cancer patients.

4.6.1.3 Formulation and administration

Chronic administration of sodium bicarbonate can lead to hypernatremia and metabolic disorders, considering the dose required in humans for polarisation when based on animal experiments where weight-based doses equate to 3 g/kg (Yang *et al.,* 2020).

4.6.1.4 Long-term safety data on the use of sodium bicarbonate

A Phase 0/I clinical trial (NCT02531919) investigated the long-term safety of sodium bicarbonate in fifteen healthy participants (Robey *et al.,* 2015). The aim was to neutralise tumour acidity and inhibit metastasis. Volunteers were enrolled to consume 0.5 g/kg/day sodium bicarbonate, divided into 2-3 doses per day, with allowed dose adjustments. The actual mean daily dose consumed was 0.17 ± 0.03 g/kg. Most adverse events were gastrointestinal-related. The study concluded that long-term sodium bicarbonate consumption is feasible and safe, but the predicted tolerable dose was too high for healthy volunteers (Robey *et al.,* 2015). Future considerations may include intra-tumour injections instead of oral administration to achieve more effective drug delivery and minimise systemic side effects (Yang *et al.,* 2020).

4.6.1.5 Pharmacological properties

After oral administration, sodium bicarbonate (NaHCO3) is absorbed into the bloodstream, leading to an increase in serum bicarbonate levels and sodium (Senewiratne *et al.,* 2024). Excess bicarbonate can cause metabolic alkalosis, a condition characterised by an elevated blood pH. Additionally, the alkalinisation of urine occurs because of increased renal excretion of bicarbonate. Pharmacokinetic studies have shown that sodium bicarbonate is widely distributed in the extracellular fluid, with an unknown half-life due to its rapid equilibration with extravascular tissues. The drug is primarily excreted in the urine, with renal elimination being the major route of elimination. Overall, the absorption, distribution, and excretion of sodium bicarbonate are critical factors in understanding its pharmacological effects and potential toxicities (Senewiratne *et al*., 2024).

4.7 Summary

Chapter Four provided a comprehensive review of the potential benefits and harms associated with the use of some of the CAMs in cancer treatment, laying the foundation for an evidence-based evaluation of their safety and efficacy. This scientific approach enables healthcare professionals to make informed decisions in clinical practice. The summarised risks associated with these CAMs are presented in Chapter Five, providing a concise overview of the potential harms related to their use. By examining both the benefits and risks, healthcare professionals can engage in informed discussions with patients, facilitating shared decision-making and optimal cancer care.

Table 4.4 Summary of information on selected Complementary and Alternative Medicines (CAMs) and considerations based on the literature

STC- 30 Superlife	
CAM	STC-30 Superlife
Reasons for CAM use	Increases energy levels
Claims	Food and Drug Administration approved, This compound (STC-30) is the origin of "stem cells" in treatment and prevention of diseases. Claims to activate the adult stem cells and provides robust immunity, cures a variety of diseases including ovarian cancer without any side effects (Erhanie *et al.,* 2022).
Reported dose **Researched dose**	● 1.5 g sachet daily ● Up to 5 g/kg daily for 30 days (Erhanie *et al.,* 2022).
Proposed pharmacokinetics and safety data	Toxicology study in rats show a significant reduction in the animals' AST levels was observed only at high doses compared to controls. Double the recommended dose has adverse effects on the kidney and haematology parameters (Erhanie *et al.,*2022).
Evidence in cancer patients	None reported
Proposed risks	Given the lack of any scientific evidence the risk, outweigh the benefit. Warnings by several Health Authorities
Grape Seed Extract – Procydin	
CAM	Grape Seed Extract-Procydin
Reasons for CAM use	Increase energy levels and enhances the immune system
Reported dose **Researched dose**	● Each tablet of Procydin contains 70 mg proanthocyanidin (Pharmacy Direct n.d.). ● 200, 400, 600, or 800 mg up to 2 g in human (Wahner-Roedler *et al.,* 2014 ● 10 to 500 mg/kg *in vivo* versus 25 *µg*/ml to 100 *µ*g/ml, *in vitro* (Olaku *et al.,* 2015)

Proposed pharmacokinetics	Proposed CYP3A4, CYP2D6 inhibition
Evidence in cancer prevention	Preclinical *in vitro* (Kaur *et al.,* 2009; Brasky *et al.,* 2011), *in vivo* (Clouatre *et al.,* 2010; Wahner-Roedler *et al.,* 2014) VITAL study, prospective, n= 35,239, 50–76 yr (Brasky *et al.,* 2011). Breast Cancer Prevention study n=46, dose escalation study by Wahner-Roedler *et al.* (2014).
Evidence in cancer treatment	*In vivo* data shows promising results (Sharma *et al.*, 2004) Limited to breast cancer cells. Preclinical studies, including *in vivo* and *in vitro* experiments, have demonstrated that grape seed extract and its constituents exhibit antineoplastic properties, characterised by induction of apoptosis (programmed cell death), anti-proliferative effects and direct cytotoxicity in various cancer cell lines (Kaur *et al.,* 2009). Flavonoids present in grape seed extract supplements have been shown to downregulate the expression of interleukin-6 (IL-6) and partially inhibit nuclear factor-κB signalling (Brasky *et al.,* 2011). Olaku *et al.* (2015) examined (*in vivo* and *in vitro*) the role of grape seed extract in preventing and treating chemo-/radiotherapy-induced toxicity. Of 41 studies, 40 showed positive outcomes when grape seed extract or grape seed proanthocyanidins were combined with chemo-/radiotherapy. Limitations: quality of study results, methodological challenges, poor and incomplete study designs.
Considerations	In human trials have been conducted as cancer prevention rather than treatment, the cohorts are small and included healthy participants. The VITAL study has certain limitations.
Evidence in cancer patients	Ongoing on Clinical Trial.gov
Proposed risks	Reactive oxygen species production with certain chemotherapeutic agents might decreased drug efficacy and proposed CYP inhibition could lead to chemotherapeutic agent accumulation and toxicity.
Rooibos tea (*Aspalathus linearis*)	
CAM	Rooibos tea (Aspalathus linearis)
Reasons for CAM use	Hydration, supports healthy bowel movements, enhances the immune system, taste sensation and relieves nausea

Recommended vs administered dose	Tea extracts at variable doses.
Proposed pharmacokinetics	Intragastric administration of midazolam in rats after two weeks of tea intake, decreased midazolam levels by 60% was due to induction of CYP3A in the tea-treated group. This could lead to CYP3A4-mediated interactions between tea and various drugs (Liu *et al.,* 2023).
Evidence in anticancer activity	Rooibos has shown to have an effect on various mechanisms such as cellular proliferation, differentiation, angiogenesis, metastasis and apoptosis in different stages of cancer. *In vivo* research indicates the anticancer activity of rooibos in skin, lung and oesophageal cancer in animals, and *in vitro* use of rooibos extract has shown to inhibit castration-resistant prostate cancer cells. (Samodien *et al.,* 2021).
Evidence in antioxidant activity	Bond and Derbyshire (2020), multiple pre-clinical studies reporting on antioxidant activity
Proposed risk	Possible induction of CYP can lead to suboptimal drug levels and anti-oxidant activity can interfere with the efficacy of chemotherapy.
***Zingiber officinale* Roscoe**	
CAM	Ginger (*Zingiber officinale* Roscoe)
Reasons for CAM use	Enhances the immune system and relieves nausea
Recommended dose **Researched dose**	● Fresh or dried rhizome: 1-4 g daily ● Fluid extracts (1:1 g/ml): 0.25-1 ml, three times daily (t.i.d.) ● Tincture (1:5): 1.25-5 ml, three times daily (t.i.d.) (Low Dog., 2010, p 325). ● Ginger extracts standardised: 5% gingerols, containing 6,8-, and 10-gingerol, 6-shogaol up to 2 g ● Ginger root: Concentrations of ginger root (0.5%-2.5%) are only detectable in serum at a starting dose of 1 g with the exception to 6-gingerol (detectable at 250 mg) (Cheng *et al.,* 2023)
Pharmacokinetics	Ginger bioactive components inhibit CYP enzymes and phosphorylated-glycoprotein transporter (Cheng *et al.,* 2023)
Evidence of anticancer properties	● Anticancer activity shown in various cancer cell lines, including colorectal and breast cancer (Ozkur *et al.,* 2022). ● A systematic review by Nachvak *et al.* (2023) analysed *in vitro* studies on ginger's anti-CRC properties, focusing on apoptotic

	pathways. Findings: Ginger and its derivatives increase B-cell lymphoma-2-associated X (BAX), increases apoptosis, decreasing BCL-2, inhibits cell proliferation, enhancing caspase activity also increased apoptosis. ● In breast cancer, 10-gingerol has shown to prevent metastasis in Triple Negative Breast Cancer and reduce proliferation in certain breast cancer cell lines (Kim *et al.,* 2022). ● Biomarker analysis from randomised clinical trials suggests that ginger supplementation (2 g/day) may reduce human telomerase reverse transcription in CRC or high-risk patients but does not significantly affect BCL-2 and BAX expression (Nachvak *et al.,* 2023).
Evidence in cancer treatment and antioxidant effects	● Preclinical studies have also demonstrated that combining ginger extract with chemotherapeutic agents like doxorubicin improves treatment outcomes in murine breast cancer models, enhancing survival rates, reducing tumour mass, and promoting apoptosis (Ozkur *et al.,* 2022) ● Danwilai *et al.* (2017) evaluate antioxidant effect and safety of ginger extract n=43 patients undergoing chemotherapy. Findings: No unacceptable toxicities, significant increase in antioxidant activity/decrease in oxidative stress. Study did not assess potential interactions between chemotherapy and ginger supplementation.
Evidence of efficacy in chemotherapy-induced nausea and vomiting	Of 16 randomised clinical trials, 8 demonstrated the positive effect of ginger treatment on the prevention and alleviation of chemotherapy-induced nausea and vomiting. Due to conflicting results, dosage variability among studies, risk of bias and limited information on chemotherapy interactions it remains unclear whether ginger is safe to use as adjuvant treatment in cancer patients (Ahn *et al*, 2020; Malossiotis *et al.,* 2024) ● The Society for Integrative Oncology recommends ginger use based on low-level evidence ● The American Society of Clinical Oncology cannot advise for or against ginger use due to insufficient evidence. The Multinational Association of Supportive Care in Cancer and European Society for Medical Oncology cannot recommend ginger as adjuvant treatment due to conflicting data, heterogeneous dosages, and non-guideline recommended antiemetic's in clinical trials
Documented adverse effects	Gastro-intestinal side effects (reflux, diarrhoea, bloating and epigastric distress (Ahn *et al.,* 2020). CYP interactions leads to documented in human accumulation of crizotinib and hepatotoxicity (Cheng *et al.,* 2023)
Considerations	Randomised clinical trials in humans with small numbers and major inconsistencies.

Proposed risk	Decreased reactive oxygen species production leading to decreased efficacy of chemotherapeutic agent, GI side effects related to ginger. CYP inhibition, as well as phosphorylated-glycoprotein leading to chemotherapeutic drug accumulation and toxicity.
Cannabis and Cannabinoid-based Agents	
CAM	Cannabis and cannabinoid-based agents
Reasons for CAM use	Pain relief, relieves nausea, enhances the immune system, calming and anticancer activity
Recommended and administered dose	The biological activity of cannabis is attributed to its constituent cannabinoids, which vary in qualitative and quantitative composition across different plant varieties (Woerdenbag *et al.,* 2023) or synthetic formulation.
Pharmacokinetics	Pharmacokinetics of cannabis vary depending on the route of administration, with different absorption properties and bioavailability of THC and CBD (Legare *et al.,* 2022). THC and CBD are highly bound to plasma proteins and rapidly distribute to well-vascularized organs and fat tissue, leading to a prolonged elimination half-life. Metabolism occurs in the liver through cytochrome P450 isoenzymes (CYP3A4, CYP2C9, and CYP2C19 for THC, and CYP3A4 and CYP2C19 for CBD) and glucuronidation by UDP-glucuronosyltransferases (UGTs). The elimination half-life of THC and CBD varies among users. CBD may interact with THC's bioavailability and metabolism, potentially inhibiting cytochrome P450 and increasing THC's effects (Woerdenbag *et al.,* 2023).
Evidence of anticancer properties	• Preclinical studies have shown potential anticancer properties of medicinal cannabis, particularly in modulating key survival and immunomodulatory factors (Brown *et al.,* 2019). • CBD and THC, have shown promise in enhancing the efficacy of first-line treatments in oncology. Findings suggest that cannabinoids may inhibit tumour growth and proliferation, induce apoptosis and autophagy, inhibit angiogenesis, migration, invasion, and metastasis, enhance the effects of antineoplastic agents, such as temozolomide and radiation and act synergistically with chemotherapeutic agents, such as docetaxel and paclitaxel (Woerdenbag *et al.,* 2023). • Ph 1b trial examine efficacy and safety of oromucosal nabiximols spray, containing synthetic THC and CBD, in combination with dose-intense temozolomide in glioblastoma patients (Twelves *et al.,* 2021). Sample size was small, results showed promising overall survival rates at 1 year, 83% in the nabiximols-treated group compared to 44% in the placebo-treated group.

	The study also found that nabiximols reduced chemotherapy-related adverse events: vomiting, dizziness, fatigue, nausea, and headache. No interactions were observed between nabiximols and temozolomide, indicating the safe use of cannabinoids with this agent. These findings warrant further investigation in an upcoming phase 2 trial to fully assess the efficacy of cannabinoids in glioblastoma treatment. • Phase II trial conducted in NZ investigated the safety and efficacy of THC-containing medicinal cannabis in patients with high-grade glioma (Schloss *et al.,* 2021). Findings: a single nightly dose of THC is well-tolerated, no serious adverse effects, improved sleep, functional well-being, and quality of life. Significant tumour reduction was observed in 9% of patients at 12 weeks, suggesting a potential anti-tumour effect when combined with standard treatment and THC/CBD oil.
Evidence of efficacy in chemotherapy- induced nausea and vomiting	• A Cochrane review by Smith *et al.* (2015) evaluated the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting. The 23 randomised clinical trials, results showed vs placebo, cannabinoids were associated with a higher chance of complete absence of vomiting and nausea. No significant difference between cannabinoids and prochlorperazine in nausea and vomiting outcomes, preference to cannabinoids vs placebo and prochlorperazine. Evidence quality was generally low to moderate; trials were at risk of bias due to design limitations and outdated chemotherapy regimens. Concluded was that cannabis-based medications may be useful for refractory chemotherapy-induced nausea and vomiting, but methodological limitations of the trials limit the confidence in the results. • PhII/III trial investigated the efficacy of adding oral THC/CBD cannabis extract to guideline-consistent antiemetic prophylaxis in adults experiencing chemotherapy-induced nausea and vomiting during moderate and highly emetogenic intravenous chemotherapy regimens. Outcomes: the difference in complete response (no emesis and no rescue medications) between THC/CBD and placebo groups. Results: a significant increase in complete response with THC/CBD (24%) vs placebo (8%), with an absolute difference of 16% (P-value 0.01). Regimens were doxorubicin/cyclophosphamide (31%) and fluorouracil/oxaliplatin (FOLFOX, 17%), 97% received corticosteroid & 5-HT3 antagonist, 80% received NK-1 antagonist, and 10% received olanzapine (Mersiades *et al*., 2023). • Conclusive evidence on THC efficacy in chemotherapy-induced nausea and vomiting was reported by Jugl *et al.* (2020) who did a systematic review of evidence for cannabis and cannabinoids as adjuvant therapy in palliative and supportive oncology care.
Evidence in cancer related pain	Cochrane review by Häuser *et al.* (2023) evaluated the efficacy and safety of cannabis-based medicines for cancer-related pain

	management. The review included 14 studies with 1823 participants, comparing cannabis-based medicines to placebo or registered analgesics. The studies assessed various cannabis-based medicines, including nabiximols (THC and CBD) and synthetic THC analogues, in different settings and cancer types. Findings: no clinically relevant benefit in pain reduction and no difference in withdrawals due to adverse events, no difference in mean pain intensity reduction when used as add-on treatment for opioid-refractory cancer pain. Low-certainty evidence for synthetic THC analogues showing superiority to placebo but not to low-dose codeine in reducing cancer pain. No added value of CBD oil in reducing pain intensity in advanced cancer patients. Results did not include studies using herbal cannabis.
Documented adverse effects	Demonstrated a favourable safety profile, with limited adverse effects (Woerdenbag *et al.,* 2023). Cannabis, THC and euphorigenic cannabinoids continuous exposure require monitoring - has been linked to the induction of psychotic symptoms in a significant proportion (20-50%) of individuals (Legare *et al.,* 2022). Symptoms can lead to cannabis-induced acute persistent psychosis. Relationship has been shown between cannabis use and exacerbated mania symptoms in patients with bipolar disorder, as well as a 3-fold increase in mania symptoms in nonclinical patients (Legare *et al.,* 2022).
Considerations	Standardisation of randomised trials, product selection, dose selection and pharmacokinetic data is a necessity to understand the efficacy safety as well as possible interactions with cancer chemotherapy.
Proposed risk	The side effects related to Cannabis or cannabinoid-based drugs. Chemotherapeutic agent interactions based on the pharmacokinetics. Cannabis interaction with Immune checkpoint inhibitors leads to worse outcomes for patients.
Cancer Bush (*Sutherlandia frutescens*)	
CAM	Cancer Bush *(Sutherlandia frutescens), "musa-pelo"*
Reasons for CAM use	Decrease tumour size, cancer fighting and alleviate pain
Recommended dose **Researched dose**	• Commercially available in 300 mg tablets Dried leaves average consumption of around 2.5-5 g of dry material or decoctions, regarded as the traditional dose of *Sutherlandia.* Highest dose of 5 g twice daily reported (Van Wyk & Albrecht, 2008) • (600 µg canavanine per capsule) twice daily (800 mg/day) for 3 months (Johnson *et al.,* 2007)

Proposed pharmacokinetics	Fasinu *et al.* (2013) investigated crude extracts of *Sutherlandia frutescens* in human liver microsomes. Results suggest concentration dependant inhibition of CYP1A2, CYP2A6, CYP2C8, CYP29C, CYP2C19 and CYP3A4/5 with little or no inhibition of CYP2D6, CYP2E1.
Tolerability or safety study	Phase I, n=25, randomised, placebo-controlled, n=12 (800 mg/day) for 3 months in healthy participants. Findings: no safety risks detected (Johnson *et al.,* 2007)
Evidence on anticancer properties	Preclinical studies demonstrate: ● inhibition of growth of hormone receptor-positive, oestrogen-dependent cell lines and stimulate MCF-12A and MDA-MB-231 cells *in vitro* (Steenkamp & Gouws, 2006), ● Induce cytotoxicity in cervical carcinoma cells (Chinkwo, 2005), ● Induce apoptosis and downregulate the Phosphoinositide 3-kinase pathway in colon cancer cells (Leisching *et al.,* 2015). ● Lin *et al.* (2016) suggests that the *Sutherlandia frutescens* extract may exert an anti-cancer effect by targeting the hedgehog pathway activity in prostate cancer cell lines of transgenic adenocarcinoma of the mouse prostate.
Documented adverse effects	None known
Evidence in cancer patients use	None reported
Proposed risk	Possible CYP inhibition.
Vitamin C (Ascorbic Acid)	
CAM	Vitamin C, *L-Ascorbic acid, ascorbate*
Reasons for CAM use	Enhances the immune system and replenishing cancer draining of vitamin C
Reported dose **Researched dose**	● 75 mg for females and 90 mg for male adults and up to 1000 mg ● Up to 4 g/kg but 3 g/kg is the tolerable dose (Böttger *et al.,* 2021).

Potential interactions	• Due to the potent antioxidant activity of ascorbic acid, administration of ascorbic acid concurrently with cytotoxic agents is avoided. Recommendations around the administration of ascorbic acid- allow five half-lives to elapse before the administration of chemotherapeutic agents. • The half-life of ascorbic acid is <2 hours in circulation based on its rapid renal clearance, allowing for IV ascorbic acid administration the day before or after chemotherapy. • For chemotherapeutic agents with effects outside of oxidative mechanisms, concurrent administration can be possible. • Human trials have shown no adverse effects when combining IV ascorbic acid with various chemotherapeutic agents like carboplatin, paclitaxel, decitabine, cytarabine, aclarubicin, gemcitabine, erlotinib, and temozolomide. In many cases, a decrease in off-target toxicity and an improvement in health-related quality of life were observed (Carr & Cook, 2018).
Evidence on anticancer activity	Anticancer activities include ascorbic acid activity as a pro-oxidant. • In vitro elicitation of hydrogen peroxide-dependent cytotoxicity within tumour cells with high dose Vit C enables reduction of the transition of metal ions, which sequentially generates hydrogen peroxide. Little human evidence is available to confirm this pro-oxidant mechanism. Another reported mechanism is the overexpression of p53 when combination therapy of ascorbic acid and certain chemotherapies are used, again suggesting ascorbic acid-mediated cytotoxicity (Böttger *et al.,* 2021; Carr & Cook, 2018). • Pre-clinical findings propose multiple mechanisms of actions of ascorbic acid in combination with cancer chemotherapy; its anticancer activity is inclusive of oxidative stress and DNA damage, decreasing antioxidant enzymes, mitochondrial stress, BCL-2 inhibition, Ten-eleven translocation-2 activation, decreasing kinase activity, p53 overexpression, adenosine triphosphate depletion, increasing iron, immunomodulation, increasing collagen and a-tubulin acetylation (Böttger *et al.,* 2021).
Documented adverse effects	Commonly reported adverse effects: hypokalaemia, hypernatremia, hypertension and anaemia. Other include kidney stones in patients with renal dysfunction (Böttger *et al.,* 2021). Findings confirmed by van Ghorkom *et al.* (2019) systematic review.
Evidence in cancer patients use	• Prospective observational studies in a meta-analysis by Harris *et al.* (2014). Findings: Results confirm a significant 19% reduced risk compared to no supplementation post-diagnosis with similar outcomes in breast cancer-specific mortality. The limitations of these results include the lack of information regarding the use of chemotherapy or radiotherapy in combination with ascorbic acid. • Data from the Life After Cancer Epidemiology study reveals contrary results with no clear benefit of ascorbic acid usage with

	chemotherapy or radiotherapy (Harris *et al.,* 2014). ● Phase I/II studies analysing the use of ascorbic acid in combination with cancer chemotherapy, inclusive of radiation therapy. The majority of the studies are dose escalation studies and show similar trends as the pre-clinical research towards positive disease control and objective response rates. Study limitations: underpowered to determine the efficacy of ascorbic acid (Böttger *et al.,* 2021). ● VITALITY Study: Phase III Study of High-Dose Vitamin C Plus FOLFOX Bevacizumab versus FOLFOX Bevacizumab in unresectable, untreated mCRC was conducted to compare the efficacy and safety of high-dose Ascorbic acid plus FOLFOX bevacizumab versus FOLFOX bevacizumab as first-line treatment in patients with mCRC. Wang *et al.* (2022) concluded that high-dose Ascorbic acid (1.5 g/kg/day) in combination with chemotherapy failed to show superior progression-free survival compared with conventional chemotherapy in chemotherapy-naive patients with mCRC as first-line treatment. ● Ongoing studies on Clinicaltrials.gov
Proposed risk	ROS interference leads to reduced chemotherapeutic agent efficacy
Considerations	Conflicting data due to biases and underpowered
Sodium Bicarbonate	
CAM	Sodium bicarbonate
Reasons for CAM use	Prevention and treatment of cancer
Dose in tablet form **Researched dose**	● 500 mg, 650 mg and 1000 mg per tablet ● 0.5 g/kg/day sodium bicarbonate, divided in 2-3 doses per day, with allowed dose adjustments. The actual mean daily dose consumed was 0.17 ± 0.03 g/kg
Pharmacokinetics	Absorption: Following oral administration, excess bicarbonate is absorbed, resulting in metabolic alkalosis and alkalinisation of urine. Distribution: Distributed in the extracellular fluid. Metabolism: Unknown half-life. Excretion in the urine and reabsorbed by the kidneys.

Management of oral mucositis	Sodium bicarbonate rinses for oral mucositis management, despite the lack of robust evidence. Non-selective use of sodium bicarbonate may lead to pH increases, potentially delaying pharmacological interventions effect (Di Fede *et al.*, 2023).
Evidence of anticancer properties	Sodium bicarbonate used as monotherapy in mice demonstrated some effect in cancer cell lines such as breast- and prostate cancer. Results from early research on mice with MCF-7 human breast cancer xenografts treated with bicarbonate-supplemented water in combination with doxorubicin shows a two-to three-fold increase in the effect of doxorubicin. The elevation of uptake of weak-base chemotherapeutic molecules could be enhanced by extracellular alkalisation Delayed tumour growth and an increase in tumour necrosis were seen in different tumour types when used in combination with other cancer therapies (Yang *et al.,* 2020).
Documented safety and adverse effects in healthy subjects	Phase 0/I trial investigated the long-term safety of sodium bicarbonate in n=15 healthy volunteers, 0.5 g/kg/day sodium bicarbonate, divided into 2-3 doses per day. Findings: Most adverse events were gastrointestinal-related. The study concluded that long-term sodium bicarbonate consumption is feasible and safe, but the predicted tolerable dose was too high for healthy volunteers (Robey *et al.,* 2015).
Level of evidence in cancer patients	NCT03910140- Ongoing (Clinical trials.gov) An early phase I, randomised, controlled, interventional study of systemic chemotherapy in combination with sodium bicarbonate for unresectable gastric cancer was registered on Clinical Trials.gov, the status on the website is listed as “unknown” and no results have been published to date.
Considerations	Lack of data to support the safe use of this CAM in cancer patients
Proposed risk	GI related adverse effects and other serious adverse effects

5 CHAPTER FIVE
DISCUSSION AND CONCLUSION

5.1 Introduction

Chapter Four provided a review of the existing literature to contextualise the study findings. The reviewed literature provided valuable insights into the potential risks associated with herb-drug interactions with selected CAMs. The literature highlighted the importance of understanding these interactions to ensure safe and effective treatment outcomes. Chapter Five provides an overview of the interpretation and implications of the study's findings and discusses the significance of the findings. Study limitations and future recommendations will also be covered for future research and practical application.

5.2 Discussion

The prevalence of CAM use in South Africa is notably lower compared to some countries around the world, as reported in the literature. The reported prevalence does support what has been shown in the literature of CAM administration rates at 14% to 91% (Escudero-Vilaplana *et al.,* 2023). The locally reported prevalence rate of Cam use may be attributed to various factors, including cultural and socio-economic differences, access to healthcare services, education and more. Studies have shown that CAM use is more prevalent in developed countries, such as the United States, Australia, and Europe, where there is greater awareness and acceptance of alternative therapies. In contrast, many developing countries, including those in Africa, might have limited access to CAM services due to the additional cost incurred. The country's healthcare framework is largely focused on conventional Western medicine, which may contribute to the lower reported use of CAM. Further research is necessary to identify opportunities for integration into the healthcare system, ensuring safe and evidence-based practice.

A growing concern is that patients often perceive plant-based remedies or products as "natural" and safe (Ektor, 2014; van Wyk & Prinsloo, 2020), but the concurrent use of complementary medicine with conventional cancer therapy poses significant risks to patients (Huebner *et al.,* 2013). The pharmacological activities and enzyme interactions of CAMs can lead to decreased efficacy of cancer drugs or increased toxicity risks (Cheng *et al.,* 2023). Nutraceuticals and complementary medicines are generally considered

dietary supplements or alternative therapies that are not subject to the same stringent regulatory approval processes as pharmaceutical drugs. Unlike registered drugs, which must undergo rigorous clinical trials before receiving health authority approval and prior to product marketing, nutraceuticals and complementary medicines can be marketed without proven efficacy in randomised clinical trials. The South African Health Products Regulatory Authority (SAHPRA) provides guidelines on the registration process of complementary medicine and relies on post-marketing surveillance to ensure safety and efficacy (SAHPRA, n.d.). This means that while some nutraceuticals and complementary medicines may have some evidence of safety and efficacy, others may not have undergone rigorous testing or may interact with other medications or have adverse effects.

The Cancer Association of South Africa (CANSA) has developed fact sheets on identified CAMs used by cancer patients, providing evidence-based information for informed decision-making (CANSA, n.d.). Decision aids, such as those developed by the Complementary Medicine Education and Outcomes (CAMEO) program research team, can support healthcare professionals (HCPs) in providing comprehensive care and promoting patient participation in treatment decision-making (Balneaves *et al.*, 2022). Decision aids are evidence-based tools promoting patient participation in treatment decision-making. Unbiased information relating to treatment options, risks versus benefits and clarity on patient values allows overall patient satisfaction upon the selection of treatment interventions. A systematic review and meta-analysis show the benefit of the use of the tools to increase knowledge in screening and treatment options (O'Brien *et al.*, 2009). The CAMEO program's seven key recommendations include communication, assessment, education, decision coaching, documentation, monitoring, and reporting adverse events related to CAM use (Balneaves *et al.,* 2022). Additionally, tools like NATMED PRO, an herb-drug interaction platform, can help identify potential interactions between herbal therapies and chemotherapeutic agents (Bazrafshani *et al.,* 2023). Collaboration between researchers and organisations like CANSA could lead to the development of decision aids and the utilisation of tools like NATMED PRO, promoting informed decision-making and safe CAM use among cancer patients. However,

considerations such as subscription fees may need to be addressed. The discussion section will provide an overview of each individual selected CAM and the potential risk posed to patients based on the scientific evidence presented during the literature review.

5.2.1 Fruits, fresh fruits, leaves, seeds and fruit extracts

5.2.1.1 STC-30 Superlife

The use of supplements that lack research-based evidence to support their claims should be approached with caution. Although patients reported using this CAM for enhanced energy levels, cancer patients should be advised against using this supplement as monotherapy or in combination with chemotherapy. The product's benefits do not outweigh its risks, and its scientific efficacy cannot be claimed without robust clinical evidence (Erhanie *et al.,* 2022).

5.2.1.2 Grape seed extract-Procydin

Despite the limited robust data, anecdotal reports from cancer patients using grape seed extract concurrently with active anticancer treatment warrant consideration. However, preclinical data are hindered by methodological concerns (Olaku *et al.,* 2015). Nevertheless, grape seed extract has demonstrated tolerability and safety in human studies, with a maximum tested duration of 11 months, suggesting potential as a complementary therapy. Further rigorous research is essential to fully elucidate grape seed extract's efficacy and safety in cancer management. The administered dose of Procydin might not have any therapeutic benefits; however, until such time that concurrent use with chemotherapeutic agents has been tested in human clinical trials, safety evidence is still lacking.

5.2.2 Herbs, herbal extracts and herbal teas

5.2.2.1 Rooibos tea (Aspalathus linearis)

The level of evidence to suggest any anticancer activity or synergistic activity of rooibos tea when used concurrently with antineoplastic agents is limited to preclinical data. Of importance is the role CYP3A4 plays as an isoenzyme responsible for the metabolism of

many anticancer therapies. Therefore, the necessity for robustness in human trials is paramount for informed decision-making and prevention of any possible toxicities. The pre-clinical data on the antioxidant activity of *Aspalathus linearis* should be considered when using anticancer treatment generating ROS, as this could lead to a decreased efficacy of the treatment. Concerning rehydration, superiority has not been reported on the rehydration effect of rooibos tea compared to water in athletes (Utter *et al.,* 2010). The proposed cancer prevention properties presented in the literature reported by (van der Merwe *et al.,* 2006) could be of consideration when future research is conducted.

5.2.2.2 Ginger (Zingiber officinale Roscoe)

Ginger *(Zingiber officinale*), a widely used CAM, has been investigated for its potential antioxidant and anticancer properties, as well as its potential to manage chemotherapy-induced nausea and vomiting in cancer patients. However, the available evidence remains inconsistent and inconclusive due to conflicting results, variability in dosage across studies, risk of bias, and limited information on potential interactions with chemotherapy (Ahn *et al.*, 2020). While some studies suggest that ginger may have beneficial effects in reducing chemotherapy-induced nausea and vomiting and oxidative stress, others have found no significant benefits. The lack of standardisation in ginger extracts, dosages, and preparation methods further complicates the interpretation of these findings. Therefore, it remains unclear whether ginger is safe and effective as an adjuvant treatment in cancer patients, and further rigorous research is necessary to fully elucidate its benefits and risks in this context.

5.2.3 Medicinal plants and medicinal plant extracts or seeds

5.2.3.1 Cannabis and cannabinoid-based medicine

Despite the plethora of research data available, the added value in curative or palliative cancer care and the possible risks involved are insufficiently proven and, therefore, a matter of debate. The translation of preclinical data to clinical applications of cannabinoids and medicinal cannabis remains challenging. The benefit versus the risk profile still seems to be poorly defined. The preferred routes of administration remain oral/sublingual

and inhaled administration, which have very different pharmacokinetic profiles. Other considerations are the medicinal plant species, synthetic preparations, dosage and frequency of use (Legare *et al.,* 2022). For refractory chemotherapy-induced nausea and vomiting, the use of cannabis or CBD has been reported as beneficial compared to placebo, but the methodological limitations of the trials limit the confidence in the results (Smith *et al.,* 2015). Recent trials compared to placebo resulted in an absolute difference in the outcomes for patients treated for chemotherapy-induced nausea and vomiting with or cannabis compared to placebo (Mersiades *et al.,* 2023).

It is important to consider the clinical effect of possible and complex interactions of cannabis products with anticancer drugs and other medicines prescribed for cancer patients. As the endocannabinoid system has been shown to play a role in tumour development and growth, it has been suggested cannabis products may be used because of their cytostatic effect against specific tumours in which cannabinoid receptors are highly expressed (Singh *et al.,* 2021). Robust clinical trials to substantiate preclinical findings are important; this will help gain a greater understanding of the utilisation of this CAM in cancer patients. Standardisation of these randomised trials, product selection, dose selection and pharmacokinetic data is a necessity to understand the efficacy safety as well as possible interactions with cancer chemotherapy.

5.2.3.2 Cancer Bush (Sutherlandia frutescens)

Findings from a review of the literature suggest that the ingestion of *Sutherlandia frutescens*, a botanical CAM, may modulate the activity of intestinal efflux transporters (phosphorylated-glycoprotein) and metabolising enzymes (cytochrome P450 isoenzymes), potentially affecting the pharmacokinetics of co-administered chemotherapeutic agents that undergo intestinal absorption. Repeated exposure to *Sutherlandia* may lead to drug accumulation and toxicity, particularly for agents with a narrow therapeutic index (Fasinu *et al.,* 2013). While preclinical studies have been conducted, robust human clinical trials are essential to evaluate the efficacy and safety of *Sutherlandia* as a concomitant therapy during cancer chemotherapy. Such evidence-

based research will inform decision-making and ensure the safe and effective use of this CAM in clinical practice.

5.2.4 Vitamins, minerals and dietary supplements

5.2.4.1 Vitamin C (L-Ascorbic acid, ascorbate)

The available data suggest that high-dose ascorbic acid supplementation is associated with positive outcomes in cancer patients, but the evidence is not yet conclusive due to the limited number of extensive randomised clinical trials and potential biases. A recent study in mCRM patients undergoing conventional chemotherapy found no superior efficacy with the addition of high-dose ascorbic acid, which contrasts with the promising preclinical findings. This discrepancy highlights the ongoing controversy surrounding the use of ascorbic acid as a complementary therapy in cancer treatment. While high-dose intravenous ascorbic acid supplementation has shown a favourable safety profile with minimal serious adverse effects, the survival outcomes in human trials do not necessarily align with the preclinical results. Standardisation and technical considerations in preclinical studies may help to clarify and consolidate the findings, leading to consistent outcomes in human trials.

5.2.5 Other practices or compounds

5.2.5.1 Sodium bicarbonate

Informed decision-making with patients is crucial, considering individual needs and medical histories. Healthcare professionals should weigh benefits against potential risks and support patients to understand the risks associated with this CAM. Due to the lack of robust evidence in this setting, this CAM should be used with caution and is considered to pose a risk to cancer patients when used with cancer chemotherapy.

5.3 Justification

The study aimed to determine the prevalence of CAM usage among cancer patients in an academic hospital in Gauteng, South Africa. The structure was as follows: Chapter One included the introduction and literature review, providing an introduction and overview of the available literature on the topic. Chapter Two described the study design

and methods used to collect the data, as well as outlined the participant selection criteria and data analysis procedures. Chapter Three provided an overview of the study findings or results, including the prevalence of CAM use among cancer patients. Chapter Four presented a review of the literature based on the selected CAMs and the existing body of knowledge to evaluate the possible risks posed by these CAMs. The last chapter (Chapter Five) concludes the study with an overview of the discussion, justification, limitations and future recommendations. This chapter allowed for the interpretation of the results and discussed their implications, justified the study's methodology and approach based on the literature and results, acknowledged the study's limitations and provided recommendations for future research and practice. The study's justification is rooted in the literature and results presented, highlighting the importance of investigating CAM use among cancer patients in the South African context.

5.4 Study limitations

- The present study's findings are constrained to the public sector, and the results cannot be generalised to the private sector due to potential differences in healthcare systems and patient populations.
- Additionally, the existing scientific literature on traditional CAMs is scarce, particularly regarding the specific chemical compositions of certain herbal mixtures reported in this study.
- The study also encountered limitations in capturing the prevalence of specific agents prescribed to manage symptoms induced by cancer treatment due to respondents' inability to recall product names and inconsistent documentation of treatments.
- Future research should consider updating the questionnaire to capture data on multiple CAM use occasions.
- Furthermore, this study's literature review was non-systematic, which may be considered a limitation. Therefore, the findings should be interpreted within these boundaries, and future research should strive to address these limitations to provide a more comprehensive understanding of CAM use among cancer patients.

5.5 Recommendations

In light of the findings and literature review, it is imperative that oncologists take a proactive approach to discussing CAM use with their patients. By identifying CAMs used by cancer patients and consulting the literature or resources such as Table 4.4 or decision aids / fact sheets for potential drug-herb interactions, healthcare professionals can support informed decision-making during cancer chemotherapy. Healthcare professionals' knowledge about CAM use in cancer patients is crucial to prevent harmful interactions. Future recommendations include editorials on unidentified products, a scoping review of commonly reported CAMs used by adult cancer patients, and the development of multilingual educational materials or decision aids to promote informed decision-making and prevent potential interactions. Additionally, a similar study in the private sector would enable a comparative analysis between the two populations and settings, highlighting similarities and differences. This would further inform evidence-based practice and improve patient care.

5.6 Conclusion

In conclusion, this study investigated the prevalence and types of CAMs used by cancer patients. A comprehensive literature review identified potential risks associated with CAM use, highlighting the importance of oncologists engaging in open discussions with their patients about CAM use. This enables informed decision-making and minimises potential risks, taking into account evidence-based information. Proactive communication is crucial to ensure safe and effective cancer management, integrating conventional and complementary practices.

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APPENDIX 1: QUESTIONNAIRE

Data collection tool

This questionnaire is designed to describe the prevalence and type of complementary and alternative medicine use amongst cancer patients receiving conventional anticancer treatment in an academic hospital in Johannesburg. The findings will assist further research and allow a better understanding behind the motivations in the selection criteria as well disclosure of CAM use.

Participant number: _____

1. PATIENT DEMOGRAPHICS

1. Sex (a) Male (b) Female (c) Other

2. Age: _____

3. Home language: _____

4. Level of education:

(a) No formal education

(b) Grade 1 to 7

(c) Grade 8 to 10

(d) Grade 11 and 12

(e) Tertiary education

5. Are you currently employed?

(a) Yes (b) No

2. DISEASE AND TREATMENT CHARACTERISTICS:

6. Diagnosis and stage of disease if known?

_____

7. Current treatment prescribed and for what period, if known?

(a) Chemotherapy

_____

(b) Radiation therapy

_____

(c) Hormonal therapy

_____

(d) Other:

_____

8. Participant still actively receiving chemotherapy/radiation

(a) Yes (b) No

3. PREVALENCE AND CHARACTERISTICS OF CAM USE

9. Do you use any natural/extra/other medicine/“muthi” not given by the doctor here at the clinic?

(a) Yes (b) No

10. If no, have you ever considered using natural/extra/other medicine/“muthi?

a) Yes b) No

11. If yes, which?

_____

12. What natural/extra/other medicine/“muthi” are you currently using?

Please explain:

_____

13. How often do you use this natural/extra/other medicine/“muthi”?

(a) daily

(b) weekly

(c) often

(d) seldom

14. How much of this natural/extra/other medicine/“muthi” do you use at a time?

(a) a teaspoon

(b) tablespoon

(c) cup / glass

(d) Tablet / pill

(e) not applicable

(f) other (specify)

_____

15. When you use this natural/extra/other medicine/“muthi”, and what does it look like?

(a) tablet or pill

(b) powder

(c) oil

(d) tea

(e) smoke

(f) injection

(g) cream

(h) not applicable

(i) other (specify)

_____

16. Where did you hear about this natural/extra/other medicine/“muthi”?

(a) family

(b) friends

(c) other patients

(d) the doctor here at the clinic

(e) another doctor

(f) staff at the hospital

(g) newspaper

(h) internet

(i) church/religious group

(j) traditional healer

(k) not applicable

(l) other (specify)

_____

17. Why are you taking this natural/extra/other medicine/“muthi”?

Please explain:

_____

18. Where do you get this natural/extra/other medicine/“muthi”?

(a) pharmacy

(b) traditional healer

(c) friends

(d) not applicable

(e) other (specify)

_____

19. Do you think this natural/extra/other medicine/“muthi” is working?

(a) Yes

(b) No

(c) Not applicable

20. How do you feel after taking the natural/extra/other medicine/“muthi”?

_____

21. Have you told your doctor or the nurses that you are using this natural/extra/other medicine/“muthi”?

(a) Yes, why?

_____

(b) No, why not?

_____

APPENDIX 2: ETHICS CLEARANCE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms I van Heerden

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210803

NAME: (Principal Investigator)	Ms I van Heerden
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Division of Pharmacology Medical School University
PROJECT TITLE:	*The evaluation and risk assessment of complementary medicine use by cancer patients treated at an academic hospital in Johannesburg*
DATE CONSIDERED:	2021/08/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr L Harmse and Professor L Maree
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/02/24

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

24/02/2022
Date

APPENDIX 3: PERMISSION TO CONDUCT RESEARCH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms. TT Mahlangu*
Email: Thandi.Mahlangu4@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 15 March 2022

GP_202111_001

Dear Mrs Izel Van Heerden

RE: PROVISIONAL APPROVAL OF STUDY

TITLE: "THE EVALUATION AND RISK ASSESSMENT OF COMPLEMENTARY MEDICINE USE BY CANCER PATIENTS TREATED AT AN ACADEMIC HOSPITAL IN JOHANNESBURG"

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.

1. Your study shall not disrupt services at the study sites.
2. Strict confidentiality shall always be observed.
3. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~
Signed by:Jayshree Punwasi
Signed at:2022-03-16 10:42:16 +02:00
Reason:Witnessing Jayshree Punwasi

Dr J. Punwasi
Clinical Director

Approved/~~Not Approved~~

Ms. G Bogoshi
Chief Executive Officer

APPENDIX 4: MEDICAL ONCOLOGY UNIT APPROVAL

FACULTY OF HEALTH SCIENCES
DEPARTMENT OF MEDICAL ONCOLOGY
7 York Road, Parktown, 2193.Johannesburg, South Africa
Telephone +27 11 488 3901
Email: jhboncology@witshealth.co.za
Charlotte Maxeke Johannesburg Academic Hospital

20 July 2021

Ms Gladys Bogoshi
CEO
CMJAH

Dear Ms Bogoshi,

RE: MS IZEL VAN HEERDEN
WITS STUDENT NO: 1949701

I hereby give Ms van Heerden permission to collect prospective patient information from the Medical Oncology Clinic in Area 495 at CMJAH.

Ms van Heerden will be doing an MSc project title: "The evaluation and risk assessment of complementary medicine use by cancer patients treated at an academic hospital in Johannesburg" under the supervision of Dr Leonie Harmse and myself.

Sincerely yours

PROFESSOR PAUL RUFF
PROFESSOR AND HEAD
DIVISION OF MEDICAL ONCOLOGY
DEPARTMENT OF MEDICINE
FACULTY OF HEALTH SCIENCES

APPENDIX 5: INFORMATION LEAFLET

Information sheet

Good day

My name is Izel van Heerden, and I am a Masters student in Medicine at the University of the Witwatersrand, Johannesburg. As part of my studies, I have to do a research project; this is why I am studying the use of other medicines/"muthi" with cancer medicine. Dr L Harmse and Prof. L Maree are my supervisors. This research project aims to find out if cancer patients are using other medicine/"muthi" with the medicine prescribed by the doctor here at the hospital. I believe that you can help me to understand what type of other medicine/"muthi" this is. Sharing this information will help doctors, nurses and pharmacists to advise patients appropriately.

As part of this project, I invite you to take part in answering a short survey; this will take around 30 minutes of your time. I will also have to collect information from your patient file, you have the right to choose if you want me to get this information or not.

No money will be paid to you for answering the questions; you will also not receive any direct benefits. If you do not want to answer the questions, there will be no downside or penalties. You may also opt out of answering any question or the study at any time. Your answers will be private, and I will not write your name on the question sheet. All the answers given by you will be stored in a safe place and not shared with anyone. If you experience any distress or discomfort at any point in this process, we will continue another time or end the interview. Support services or counselling will be available to you free of charge if you need to speak to a counsellor after you have taken part in the survey. The name of the counsellor is Dr Nokuthula Nikosi-Mafutha and her contact details are 011 488 3094, nokuthula.nikosi-mafutha@wits.ac.za

If you have any questions during or afterwards about this project, you can contact me or my supervisors using the details below. This study will be written up as a dissertation that will be available online through the university library website. If you have any concerns or complaints regarding the ethical procedures of this study, you are welcome to contact the University Human Research Ethics Committee (Medical), Professor Clement Penny by telephone, 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.

Yours sincerely,

Researcher:

Mrs. Izel van Heerden, email: 1949701@students.wits.ac.za, 082 827 7299

Supervisors:

Dr Leonie Harmse, Leonie.harmse@wits.ac.za, 011 717 2637

Prof. Lize Maree, Lize.Maree@wits.ac.za, 011 488 4272

APPENDIX 6: INFORMED CONSENT

Appendix 3: Consent form

I hereby confirm that the external researcher, Izel van Heerden (who is not employed by the hospital), has informed me about the nature, conduct, benefits and risks of the study titled: "The evaluation and risk assessment of complementary medicine use by cancer patients treated at an academic hospital in Johannesburg". I have read the information, or it has been read to me. I have had the opportunity to ask questions about it, and all of my questions have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

I have also decided to give / deny consent to my personal details, which would include medical records relevant to my condition and treatment, may be shared with the researcher and that this information will only be used for this study. I am aware that the results of the study, including personal details regarding my age, date of birth, initials, diagnosis and treatment will be anonymously processed into a study report.

In view of the requirements of the research, I agree that the data gathered during this study can be accessed by the supervisor and other authorities.

I may, at any stage, without prejudice, withdraw my consent and participation in the study.

A copy of this Informed Consent form has been provided to me.

Participant:

_____	_____	_____
Printed Name	Signature/Mark/Thumbprint	Date and Time

Witness (if applicable):

_____	_____	_____
Printed Name	Signature/Mark/Thumbprint	Date and Time

Researcher:

_____	_____	_____
Printed Name	Signature/Mark/Thumbprint	Date and Time

Izel van Heerden.docx

ORIGINALITY REPORT

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