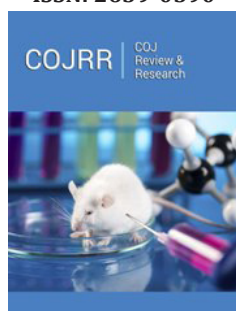


A Brief Review of Secondary Plant Metabolites as Anticancer Agents

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ISSN: 2639-0590



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Submission:  April 09, 2020

Published:  May 18, 2020

Volume 2 - Issue 4

How to cite this article: Naicker L, Mohanlall V. A Brief Review of Secondary Plant Metabolites as Anticancer Agents. COJ Rev & Res. 2(4). COJRR.000545.2020. DOI: [10.31031/COJRR.2020.02.000545](https://doi.org/10.31031/COJRR.2020.02.000545)

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Abstract

Plants have provided a source of medicine from the beginning of human history and are the core of modern medicine. Moreover, plant-based drug discovery has led to the development of various anticancer drugs (such as vincristine, vinblastine, etoposide, paclitaxel, camptothecin, topotecan and irinotecan). The use of botanical, photochemical, biological and molecular techniques have facilitated the discovery of novel secondary metabolites from native and indigenous plants that can inhibit the human topoisomerase II enzyme (target for anticancer drugs) and kill cancer cells. Therefore, the aim of this review was to further investigate the anticancer activity of secondary metabolites from native and indigenous plants and determine the classes of compounds that contributed towards its activity.

Keywords: Anticancer; Secondary metabolites; Topotecan; Etoposide; Vincristine

Introduction

Thousands of years ago, ancient civilizations in many countries such as China, India and Thailand used plants for medicinal purposes [1-3]. The traditional use of plants has continued into modern times as the World Health Organization (WHO) estimated that 80% of people living in developing countries depend on traditional medicine (mostly herbal medicines) to fulfill their primary health care needs [4]. Moreover, herbal medicines are highly valuable in the international marketplace. In Western Europe, herbal medicine revenue amounted to US \$5 billion in 2003-2004. In China, sales of herbal medicine products reached US \$14 billion in 2005. In Brazil, herbal medicine revenue reached US \$160 million in 2007 [4]. Locally, over 70 plant species are used in Africa to treat both veterinary and human patients [5]. In addition, South Africa has a long history of using plants in traditional healing as it hosts a variety of around 30,000 flowering species [6].

This accounts for almost 10 % of the world's higher plant species [7]. Thus, plants have been an integral component of the health care system both locally and internationally. There are several advantages to using plants for treat cancer. The complex synergistic interaction of various compounds in plants allows for the designing of herbal formulations that attack cancerous cells without harming normal cells of the body. This is possible as some plants can protect the body against cancer by enhancement of its detoxification functions. Certain plants contain biological response modifiers that can prevent the growth of cancer by modulating the activity of specific hormones and enzymes. Some plants have good immunomodulatory and antioxidant properties which can promote anticancer activity [8,9].

Moreover, a survey documented that over 60% of cancer patients depend on the use of vitamins or herbs as therapy [10]. Therefore, medicinal plants play an important role in the treatment of cancer. Although traditional practices involve the use of complex plant extracts, scientists have focused on purifying and identifying Independently Active Compounds (IACs) from plant extracts. The advantage is that once the structures of the IACs are determined they can be chemically or semi- chemically synthesized. The disadvantage is that some compounds found in plants act in a synergistic manner with other compounds to bring about biological activity.

Plants produce two distinct groups of compounds. The first group consists of the primary metabolites which include sugars (constituents of structural and nutritional elements), amino acids (constituents of structural elements and enzymes), lipids (constituents of membranes and nutritional elements) and nucleotides (constituents of genes). These metabolites are needed for the growth of the plant [11]. The second group consists of the secondary metabolites which include five types of compounds: polyketides, isoprenoids (terpenoids), alkaloids, phenylpropanoids and flavonoids (polyphenols) [12]. They are responsible for metabolic and/or growth regulation, lignification, the colouring of plant parts and protecting the plant against pathogen attack. Secondary metabolites are important constituents as they possess pharmaceutical properties [11,13]. Thus, these compounds are responsible for any possible anticancer activity.

Scientists have discovered many anticancer compounds from plants. A classic example is the discovery of a diterpene known as taxol which was isolated from the Pacific yew tree, *Taxus baccata*

[13]. This research began in 1958 when the National Cancer Institute (NCI) (United States of America) screened 35,000 plants for anticancer activity. Fortunately, a breakthrough was made in 1963 when Drs M. Wall and M.C. Wani of the Research Triangle Institute (North Carolina) found that the extract from the bark of *T. baccata* exhibited anticancer activity [14]. Twenty years later human clinical studies began and taxol was shown to be active against ovarian cancer which was incurable during the 80's. In order to further develop taxol, the NCI issued a contract to Bristol Myers- Squibb in the United States [15]. Nowadays Taxol is semi-chemically synthesized as paclitaxel by using the needles and twigs from yew species which are cultivated under agricultural conditions. This drug has been approved by the Food and Drug Administration (FDA) for treating ovarian, breast, lung and other types of cancers. It is sold under the trade name Taxol [13]. Table 1 shows other plant-derived anticancer compounds that have been commercialized. South Africa has a variety of anticancer plants (Table 2) [13-36].

Table 1: Plant-derived anticancer compounds that have been commercialized.

Plant	Traditional use/s	Parts used	Commercial Products	References
<i>Camptotheca acuminata</i> (Camptotheca)	Used to treat stomach and liver cancer as well as leukaemia.	Bark, wood and young leaves.	Three semi-synthetic drugs have been derived from camptothecin. These have been approved by the FDA: 1) Topotecan is used to treat advanced ovarian cancer. It is marketed under the trade name Hycamtin. 2) Irinotecan HCl is used to treat metastatic cancer of the colon or rectum. This drug was approved in June 1996. It is sold under the trade name Camptosar. 3) 9-nitro camptothecin is used to treat pancreatic cancer. It is sold under the trade name Rubitecan.	[13]
<i>Podophyllum peltatum</i> (Mandrake American)	North American Indians used the plant as an emetic and vermifuge.	Root and resin.	Etoposide is one of the most active drugs for the treatment of small-cell lung cancer and testicular carcinoma. It is also active against oesophageal, gastric, prostatic, ovarian and non-small cell lung cancer as well as chronic and acute leukemia. Etoposide is used as etoposide phosphate. It is sold under the trade name Etopophos.	[13,16]
<i>Vinca rosea</i> Linn. (Periwinkle)	Used to treat skin disorders, cramps, diabetes, high blood pressure, asthma, constipation and menstrual problems.	Leaves stem and flower buds.	Two Vinca alkaloids are used in the treatment of cancer: 1) Vincristine is used to treat childhood's leukaemia, Hodgkin's disease and other lymphomas. 2) Vinblastine is used to treat testicular cancer, breast cancer, Kaposi's sarcoma, Hodgkin's disease and other lymphomas.	[13,17,18]
<i>Taxus baccata</i> (Yew)	Played a role in religious practices as temples were built around Yew trees to serve as places of worship.	Stem segments, needles (1-2 cm long) and roots.	Taxol is semi-chemically synthesized as paclitaxel. This drug is used to treat ovarian, breast, lung and other cancers. It is sold under the trade name Taxol.	[13]

Table 2: South African plants that have shown to exhibit anticancer activity.

Plant	Traditional uses	Active compound	Cancer line/s	References
<i>Sutherlandia frutescens</i> (Cancer bush or kankerbos)	Wounds, fevers, chickenpox, stomach problems, eye troubles and cancer.	L-canavanine	MIA PaCa-2 (Pancreatic cancer).	[19-23]
<i>Aloe ferox</i> (Cape aloe or bitter aloe)	Skin and hair treatments, constipation, hypertension, stress, arthritis, conjunctivitis, toothaches, sinusitis and stomach pains.	Aloe-emodin	SJ-N-KP (Neuroblastoma), Hep G2 and Hep 3B (liver cancer cell lines).	[24-29]
<i>Withania somnifera</i>	Wounds, abscesses, inflammation, haemorrhoids, rheumatism and syphilis.	Withaferin A	MCF-7 and MDA-MB-231 (breast cancer cell lines).	[30,31]

<i>Tulbaghia violacea</i> (Wild garlic)	Oesophageal cancer.	Methyl- α -D-glucopyranoside	MCF7 and HeLa (cervical cancer).	[32-34]
<i>Prunus Africana</i>	Benign prostatic hyperplasia.	Ethanollic bark extract	PC3 and LNCaP (Prostate cancer cell lines).	[35,36]

Treatment of cancer

The treatment of cancer can involve surgical intervention, radiation, chemotherapy, targeted therapy and/or other therapies [37]. The objective of any cancer treatment is to remove all cancerous tissue without harming normal tissues. Severe cases of cancer are treated by surgery which allows for the removal of cancerous tissue with less damage to healthy tissues but surgery can also have certain risks (such as bleeding, drug reactions and damage to nearby tissues or organs) and side effects (such as pain and infection) [38,39]. In less severe cases of cancer, radiation or chemotherapy can be used to remove the cancerous tissue but these treatments are limited due to the toxicity imposed on healthy tissues [40].

The side effects of radiation therapy depend on the part of the body that is exposed to the treatment. The following side effects may be experienced: diarrhoea, hair loss, fatigue, mouth and throat changes, nausea, vomiting, sexual changes, fertility changes, skin changes and urinary changes [41]. The side effects of chemotherapeutic drugs may include: anemia, appetite changes, bleeding problems, constipation, diarrhoea, fatigue, hair loss, infection, memory changes, mouth changes, throat changes, nausea, vomiting, nerve changes, pain, sexual changes, fertility changes, skin changes, nail changes, swelling and urination changes [42]. In addition, a major complication that can occur while chemotherapy is administered is multi-drug resistance (MDR). This occurs as a result of

- The up-regulation of membrane proteins which pump the drugs out of the cell to decrease the intracellular drug concentration,
- The interruption of the balance between bioactivation and detoxification pathways,
- Alterations in DNA repair response and

D. Alterations in apoptosis response. Thus, MDR can hinder the success of treating cancers by chemotherapy [43].

On the other hand, some cancers are treated with targeted therapy. This involves the use of monoclonal antibody drugs which target and disrupt molecular pathways that are responsible for promoting tumorigenesis [44]. However, some of these drugs are associated with serious side effects. For example, trastuzumab causes cardiotoxicity in women with metastatic breast cancer [45]. Cetuximab and panitumumab are used for the treatment of refractory metastatic colorectal cancer but these drugs cause a skin rash on the face and upper torso [46]. Rituximab is used to treat non-Hodgkin's lymphoma but it is associated with serious infections such as the John Cunningham virus which infects the central nervous system [47,48]. Hence due to the side effects caused by the current cancer treatments, there is a need to discover and develop new drugs to effectively and safely treat cancer.

How do anticancer drugs induce apoptosis?

Anticancer drugs are classified according to their mechanism of action. There are four main classes of anticancer drugs: antimetabolites, genotoxic agents, anti-mitotic agents and targeted therapies [49,50] (Table 1). Through their mechanism of action, anticancer drugs can initiate apoptosis by switching on the expression of signal molecules such as Fas and FasL (for initiation of the extrinsic pathway type I and II) or p53 (for initiation of the intrinsic pathway) [51]. For instance, emodin induces topoisomerase II inhibition which causes DNA damage that activates the expression of FasL for initiation of the extrinsic pathway type I [52]. On the other hand, 6-Mercaptopurine incorporates itself into DNA and subsequently activates the expression of p53 for initiation of the intrinsic pathway [53]. Thus, anticancer drugs work in a very intricate manner to facilitate the death of cancer cells (Table 3) [54-60].

Table 3: Classes and mechanisms of anticancer drugs.

Class	Mechanism of action	Example of a drug	Reference
Antimetabolites	Interferes with the function of metabolites that are involved in normal metabolism.	Gemcitabine- Pancreatic cancer Methotrexate- Acute lymphoblastic leukaemia 6-Mercaptopurine- Acute lymphoblastic leukaemia	[54-57]
Genotoxic agents	Causes DNA damage by reacting with DNA or by targeting enzymes that are essential for DNA replication (for example, topoisomerases).	Cisplatin- Sarcomas Epirubicin- Breast and ovarian cancer Doxorubicin-Breast cancer	[56-58]
Anti-mitotic agents	Disturbs the mitotic progression of cells by interfering with their microtubules (organelles that are responsible for controlling cell division by mitosis).	Paclitaxel- Ovarian, breast, lung and other cancers	[13,50]
Targeted therapies	Inhibits biochemical pathways and mutant proteins that are essential for tumour growth and survival.	Imatinib- Chronic myeloid leukaemia and certain acute lymphoblastic leukemia Gefitinib- Non-small cell lung cancer Bortezomib- Multiple myeloma and mantle cell non-Hodgkin's lymphoma	[49,59,60]

Conclusion

Anticancer treatment and therapy have evolved significantly since the 1820s when Dr James Arnott introduced cryotherapy as a mechanism to freeze tumors in breast and uterine cancer patients. Radiotherapy and immunotherapy were the main pillars of treatment for cancers in the late 19th century until the introduction of the chemotherapeutic drug, Mustine in 1942. The introduction of plant metabolites has contributed to the improvements in outcomes related to the treatment of cancer. Advances in phytochemical characterization and understanding the pharmacokinetic properties of plant metabolites are proving effective to increase the survival rate of cancer patients. New discoveries in the identification of novel metabolites from plants and novel targets in cancer cells are of paramount importance to our successful treatment of cancer.

Acknowledgement

The authors wish to thank the Durban University of Technology and the Department of Higher Education and Training (DoHET) for providing facilities and the National Research Foundation (NRF) for funding.

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