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# Identification and Utilization of Pharmaceutically Novel Chemicals from Plants for the Treatment of Cancer – A critical Appraisal

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***Abstract***

*Cancer remains to be one of the leading causes of death around the world. The advent of modern drug-targeted therapies has undeniably improved cancer patients' cares. Cancer chemoprevention with natural phytochemical compounds is an emerging strategy to prevent, impede, delay, or cure cancer. Because, majority of the anticancer drugs currently available in the market are natural products or their analogues. This review summarizes the research in cancer chemicals from plants and treatment using the bioactive components from natural plants. It is suggested that there is a need for further investigation to isolate active principles which confer the pharmacological action. This is in turn helpful in production of safer drugs in the treatment of various ailments including cancer.*

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## Introduction

Since time immemorial, plants have provided humans with medicines. Plants are also the basis of a wide variety of goods ranging from food, phytopharmaceuticals, herbal remedies, perfumes, cosmetics, colouring agents, detergents, liqueurs, varnishes, fireworks, to detergents. According to World Health Organization estimates, over 80% of people in developing countries depend on traditional medicines for their primary health needs (Farnsworth and Soejarto, 1991). The fossil details at the famous burial site in the Shanidar Cave in the northern part of Iraq reported that, Neanderthal (*Homo neanderthalensis*) remains have been found to contain residues of medicinal herbs about 60,000 years ago, which indicate that natural products had been used even before the available evidence (Solecki, 1975; Holt and Chandra, 2002). The more recent discovery of the 'Iceman' on the Italian-Austrian border in the Alps provides intriguing evidence of early use of medicinal fungi in Europe. This hunter, who had been lying well preserved in the ice for about 5300 years, was found to be in possession of a fungus, the birch polypore (*Piptoporus betulinus*), which is known to have purgative and antibiotic properties, and which he might well have been using to treat the whipworm infestation of his intestines (Heinrich et al., 2004).

The Chinese *Pen Ts'ao*, which was written 4800 years ago, the oldest known document concerning medicinal plants (no less than 360 plants). This suggests that herbal medicine was already at an advanced stage in China at this time (Mann, 1992). In Mesopotamia (part of present-day Iraq), 4600-year old clay tablets inscribed with cuneiform characters have been found that contain references to familiar medicinal plants such as myrrh, liquorice and the opium poppy (Cragg and Newman, 2002). Certainly many of these products are modified and are still used (Nakanishi, 1999a, 1999b; Cragg and Newman, 2001a, 2001b). Another famous early document detailing the use of plants as medicines is the Ebers papyrus from Egypt, which was written about 3500 years ago (Mann, 1992).

Ayurveda (Indian system of medicine) has also contributed an extensive literature to the traditional system of medicine. From 6th Century BC to 7th Century AD there was systematic development in the Ayurvedic science and it is called Samhita period, when a number of classical works (Caraka Samhita, Susruta Samhita, Astanga Samgraha, Astanga Hridaya and Bhela Samita) were produced by several authors and during this period there existed systematized medical care (Narayanaswamy, 1981). Until the early nineteenth century the crude extract of the plant in various forms had been used for treatment. Later with an advent in technology in the field of analytical chemistry and acquiring exhaustive knowledge in science, the isolation and purification of active ingredients from medicinal plants were practiced, which demonstrated their value in medicine (Drews, 2000). In 1815, morphine

was isolated from opium extract (Serturner, 1817), followed by the isolation of papaverin from opium in 1848 (Sneader, 1985).

**Ethnopharmacology and phytotherapy**

Ethnopharmacology is a multidisciplinary field devoted to the study of pharmacologically active agents traditionally used by humans. The term ethnopharmacology was coined as recently as 1967 by Efron, who used the term in the context of hallucinogenic substances (Heinrich and Gibbons, 2001). More recently, ethnopharmacology has been defined as *"... the interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man"* (Bruhn and Holmstedt, 1981). The term phytotherapy is used to describe the use of plant-based, chemically complex therapeutic agents in contemporary, mostly industrialised societies. Phytotherapy is usually based on a history of traditional use, but it differs from traditional indigenous herbal medicine by employing industrialised extraction and manufacturing methods and by being cosmopolitan in scope. Hence, phytomedicines made from plants from around the globe are available in most industrialised countries. Till recently around 35,000 to 70,000 plant extracts have been screened for their medicinal applications (Farnsworth and Soejarto, 1991). These extracts are not only used as direct drugs but are also used as a precursor for the synthesis of new drugs with improved pharmacological properties (Ballabh *et. al.*, 2008). In the last century medicinal plants were considered to be the chief source of natural products because several active compounds have been isolated from different plants (Qin and Xu, 1998; Lee, 1999). Some of these compounds include vinblastine, vincristine, etoposide, teniposide, paclitaxel, docetaxel, topotecan, and irinotecan that are approved in USA as anticancer agents (Lee, 1999).

**Inflammation**

Inflammation is being implicated in the pathophysiology of an increasing number of diseases. In addition to conditions traditionally considered to be inflammatory in nature, inflammation is now considered to have a role in a wide range of pathologies, including cardiovascular disease (Hansson, 2005; Kaperonis *et. al.*, 2006), cancer (Zhang and Rigas, 2006), diabetes (Deans and Sattar, 2006; Duncan and Schmidt, 2006), age-related macular degeneration (Rodrigues, 2007), Parkinson's disease (Hald *et. al.*, 2007), Alzheimer's disease (Eikelenboom *et. al.*, 2006), and possibly depression (Kulmatycki and Jamali, 2006).

**Arachidonic acid metabolism**

Products of arachidonic acid metabolism such as prostaglandins and leukotrienes play key roles in inflammation, and their syntheses are well established targets in the pharmacological treatment of inflammation. Arachidonic acid (5*Z*,8*Z*, 11*Z*,14*Z*-eicosatetraenoic acid) is an unsaturated, 20-carbon, omega-6 fatty acid found in cell membranes. It can be obtained from the diet or be derived from linoleic acid.

In the cell membrane, arachidonic acid is esterified to phospholipid, and arachidonate must be liberated from phospholipid before it can act as a substrate for enzymatic modification. These modifications, catalysed by various enzymes, are known as arachidonic acid metabolism and can lead to the formation of inflammatory mediators collectively known as eicosanoids, i.e. prostaglandins (PGs), thromboxanes (TXs), hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs) (Calder, 2005; Eberhart and Dubois, 1995).

Arachidonic acid is released from the cell membrane by phospholipase enzymes, in particular phospholipase A2, and the free acid can be metabolised to eicosanoids by cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Metabolism catalysed by COX enzymes gives rise to prostaglandins of the 2-series as well as thromboxanes, while LOX metabolism leads to the formation of leukotrienes (Fig. 1).

**Plants as anti-cancer agents**

*When you examine a man with an irregular wound...and that wound is inflamed...[there is] a concentration of heat; the lips of that wound are reddened and that man is hot in consequence...Then you must make cooling substances for him to draw the heat out...leaves of willow.*(Translated entry from the Ebers papyrus, as quoted in Mann, 1992)

Cancer is a pathological condition characterized by unregulated cell proliferation, spread of abnormal cells and lack of apoptosis that result in death if not controlled (Sasikumar *et. al.*, 1999; Wyllie *et. al.*, 1999; Reed, 1999). Cancer occurs as a result of repeated mutations in specific regions of DNA and escape of the mutated genes from destruction in cell cycle regulation (Gibbs, 2003). For cancer, chemotherapy is the preferred strategy to treat the disease with some limitations due to its side effects. The natural compounds have least side effects. Hence, several anticancer compounds isolated from various plant species can be considered as a safe alternative for synthetic drugs.

Epipodophyllotoxin isolated from the roots of *Podophyllum peltatum* exhibited strong anti-tumor activity (Stahelin, 1973). This was the beginning of natural products as anticancer compounds roughly began in 1947 (Geetha *et. al.,* 2007). Two alkaloids namely vinblastine and vincristine (Fig. 2) isolated from the plant *Catharanthus roseus* are used for treating a variety of cancers.

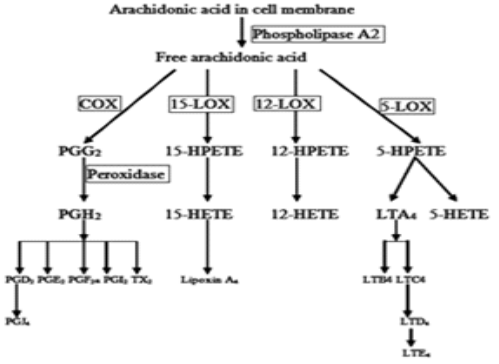
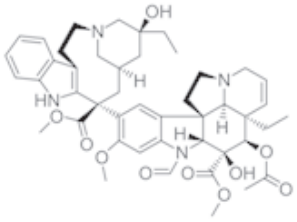
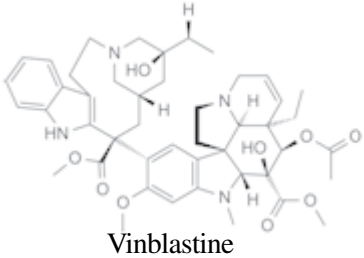



*Fig. 1: Schematic representation of the metabolism of arachidonic acid catalysed by cyclo-oxygenase (COX) and lipoxygenase (LOX) enzymes.*

including leukemia, lymphoma, breast and lung cancers (Cragg and Newman, 2005), and it was first isolated and marketed in 1961 (Geetha *et. al.,* 2007). Similarly a diterpenoid compound, Paclitaxel isolated from the bark of the pacific yew, *Taxus brevifolia* is significantly active against ovarian cancer, breast cancer and lung cancer (Rowinsky *et. al.*, 1992). Camptothecin isolated from the Chinese ornamental tree *Camptotheca acuminata* is used for the treatment of Ovarian and lung, ovarian, breast, pancreas and stomach cancers (Sriram *et. al.*, 2015) (Table 1). Similarly, eight compounds isolated from various extracts of *Tinospora cordifolia* had high anticancer potential. The compound palmatine was active against KB and HT-29; tinocordiside against KB and CHOK-1; yangambin were active only against KB cell line. Additionally *N*-formylannonain and 11-hydroxymustakone, exhibited immunomodulatory activity (Bala *et. al.*, 2015).



Vincristine

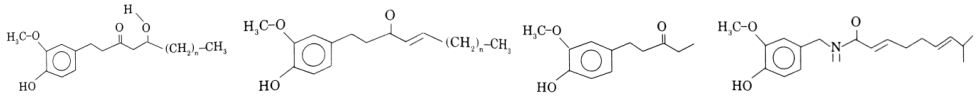


Vinblastine

*Fig.2: Chemical structure of the important anticancer chemicals of Catharanthus roseus*

Two pure compounds gallocatechin and epigallocatechin extracted from *Mimusops elengi* exhibited satisfactory anti HIV-1 activity (Suedeea *et. al.*, 2014). The ethanolic extract of the whole plant of *Couroupita guianensis* exhibited wound-healing capacity by decreasing the surface area of the wound and increasing the tensile strength (Umachigi *et. al.*, 2007). Similarly, various extracts of flowers and bark of *Couroupita guianensis* showed that flowers have relatively more analgesic property than bark. Additionally both the extract exhibited significant anti-inflammatory activity against carrageenan induced inflammation (Geetha *et. al.*, 2004). The leaf and flower extract of *Guazuma ulmifolia* exhibited gastroprotective effects in Wistar rat model of acute gastric ulcer induced by diclofenac. This protection against injury was mainly due to anti-inflammatory and radical-scavenging mechanisms (Berenguer *et. al.*, 2007). *Nerium oleander* possesses anticancer and anti-inflammatory activities, attributed to the triterpenes present in this plant (Zhao *et. al.,* 2007).

Ginger (*Zingiber officinale*) hot water extract inhibited the activities of cyclooxygenase and lipoxygenase in the arachidonic acid cascade by suppressing the prostaglandins and leukotrienes (Bliddal *et. al.,* 2000). The active constituent responsible



Gingerol Shogaol Zingerone Capsaicin

*Fig.3: Chemical structure of the important constituents of ginger*

for anticancer and anti-inflammatory activities may be (6)-shagaol and gingerol (Sharma et al., 1994; Park *et. al.,* 1998) (Fig. 3). Gingerol has been studied for its anticancerous effects for the tumors in colon (Jeong *et. al.,* 2009), breast and ovarian (Rhode *et. al.*, 2007; Lee *et. al.,* 2008) and pancreas (Park *et. al.,* 2006) (Fig. 3).

Table 1: Important plants known to yield anticancer drugs*

| Plants | Anticancer drugs | Mode of action |
|---|---|---|
| *Catharanthus roseus* (Apocynaceae) | Vincristine, Vinblastine | Used in acute in children and adult lymphoma, testicular carcinoma |
| *Betula alba* (Betulaceae) | Betulinic acid | Combats melanoma |
| *Thalictnum minus, T. dsycarpum, T. glandulosissimum* (Ranunculaceae) | Hernandezine, thalicarpine | Antileukaemic, effective against sarcoma cells |
| *Camptotheca acuminata* (Nyssaceae) | Camptothecin | Active against solid epithelial tumours, lymphoma and leukaemia |
| *Colchicum speciosum* (Liliaceae) | Colchicine | Combats breast, thyroid and oesophagus cancers |
| *Cephalotaxus harringtonia* (Cephalotaxaceae) | Harringtonine, homoharringtonine | Antileukaemic, cambats agranulocyte and myelocytic leukaemias |
| *Tripterygium wildfordii* (Celastraceae) | Triptolide A,B,C, Tripdionide | Combats leukaemia |
| *Brucea antidsentrica* (Simaroubaceae) | Bruceantin | Combats breast cancer, melanoma sarcoma |
| *Podophyllum peltatum* (Podophyllaceae) | Podophyllotoxin | Antineoplastic agent, effective against germ cell neoplasm, lung metastatic tumours, malignant lymphoma and carcinoma of nasopharynx |
| *Taxus brevifolia* (Taxaceae) | Paclitaxel (Taxol) | Combats ovarian and breast cancer |
| *Blekeria vitensis* (Apocynaceae) | Ellipticine | Combats breast cancer |
| *Maytenus serrata* (Celastraceae) | Maytansine | Antileukaemic |

* Adapted from Alexandrova *et al.* (2000) and Geetha *et al.* (2007)

The anticancer activity of *Andrographis paniculata* in human cancer and immune cells was studied. Andrographolide, the major constituent of this plant, exhibited anticancer activity on diverse cancer cells (Rajagopal *et. al.,* 2003; Kumar *et. al.,* 2004). Several other compounds such deoxydi hydroandrographolide, deoxyandro

grapholide, neoandrographolide and andrographolide showed anti-inflammatory activity (Pramanick *et. al.,* 2007).

Catechin from *Camellia sinensis* (Theaceae), administered to pheochromocytoma cells was active (Akagi *et. al.*, 1997). Coconut cake shows anticarcinogenic effect in the rat which colon cancer induced by 1, 2-dimethylhydrazine (Nalini *et. al.,* 2004).

Curcumin (diferuloylmethane) is the major components of popular Indian spice turmeric, *Curcuma longa* L.*,* a member of the ginger family. Its anti-cancer effects have been studied for colon cancer, breast cancer (Bachmeier *et. al.*, 2010), lung metastases, and brain tumor (Senft *et. al.,* 2010).

Apigenin is a flavone present in vegetables such as parsley, celery, chamomile (Hoensch and Oertel, 2011), and Egyptian plant *Moringa peregrina* (El-Alfy *et. al.,* 2011). It demonstrates cytotoxic activities against breast cancer cell lines (MCF 7), colon cell line (HCT 116), and its cytotoxic activity is comparable to that of doxorubicin (El-Alfy *et. al.,* 2011; Wang *et. al..,* 2012).

Saffron is a spice from the flower of the *Saffron crocus* and a food colorant present in the dry stigmas of the plant *Crocus sativus* L. It is listed as a potential agent for a novel anti-cancer drug against hepatocellular carcinoma (Abdullaev and Espinosa-Aguirre, 2004; Amin *et. al..,* 2011; Gutheil *et. al.,* 2011), human lung cancer (Samarghandian *et. al.,* 2010, 2011), pancreatic cancer cell line (Bakshi et al*.,* 2010), skin carcinoma (Das *et. al..,* 2010), colorectal cancer cells (Aung *et. al..,* 2007) and breast cancer (Chryssanthi *et. al..,* 2011).

**Conclusion**

Plant products have contributed a lot to the development of various drugs especially cancer therapy and many cancer patients rely on these natural products for relief. The identified chemicals for cancer therapy are just a 'tip of the iceberg', yet lot more compounds from plants awaiting its discovery. Systematic screening of these chemicals may be rewarding in the search of better cancer therapeutic agents.

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