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REVIEW ARTICLE

Anticancer and chemopreventing natural products: some biochemical and therapeutic aspects

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Summary

Natural products have afforded a rich source of compounds that have found many applications in cancer chemotherapy. Furthermore, the vast structural spectrum of natural compounds can provide "lead compounds" for therapeutic improvement by molecular modification. Over 70% of anticancer compounds are either natural products, or natural product-derived substances. On the other hand conjugation of toxic natural products to monoclonal antibodies or polymeric carriers can lead to more efficacious targeted therapies. Since less than 15% of higher plants have been systematically investigated, the natural products research towards chemotherapy requires further attention and multi-scientific collaboration. An enforcing application to chemotherapy, using natural products, is also chemoprevention. Apart from vegetables and fruit, more than 1,000 different phytochemicals are already proved to possess interesting chemopreventing activities. Effectiveness of chemopreventing agents reflects their ability to counteract certain upstream signals that leads to genotoxic damage, redox imbalances and other forms of cellular stress. Chemoprevention by edible phytochemicals is now considered to be an inexpensive, readily applicable, acceptable and accessible approach to cancer control and management. The present short review deals with a number of recent biochemical and therapeutic routes, concerning current approaches towards natural anticancer agents in clinical practice, new candidate oncotherapy drugs from plants, marine and microorganisms, as well as promising chemopreventing agents from nature.

Key words: anticancer, biochemistry, chemoprevention, natural products, therapeutics

Introduction

Cancer is a growing health problem around the world, particularly with the steady rise in life expectancy, increasing urbanization and the subsequent changes in environmental conditions, including lifestyle. According to a recent report by the World Health Organization, there are now more than 10 million cases of cancer per year worldwide.

Natural products in general have been the most significant source of drugs in science.

Throughout history, natural products have afforded a rich source of compounds that have found many applications in the fields of medicine, pharmacy and biochemistry. Within the sphere of cancer, a number of important new commercialized drugs have been obtained from natural sources, by structural modification of natural compounds, or by the synthesis of new compounds, designed following a natural compound as model. The huge structural diversity of natural compounds isolated from plants, marine species and microorganisms can provide "lead compounds" for therapeutic improvement by molecular modification. Additionally, semi-synthesis processes of new compounds, obtained by molecular modification of the functional groups of lead compounds, are able to generate structural analogues with greater pharmacological activity and with fewer side effects [1].

Their dominant role in cancer chemotherapeutics is clear with about 70% of anticancer compounds being either natural products, or natural product-derived, and may serve as models for the preparation of more efficacious analogs using chemical methodology such as total or combinatorial (parallel) synthesis, or manipulation of biosynthetic pathways [2].

The fact that about 7 million people die from vari-

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ous types of cancer every year, making this disease responsible for 12.5% of deaths worldwide, raises an overwhelming demand to develop new, more potent and effective, anticancer as well as chemopreventing agents [3].

In 1960, the National Cancer Institute (NCI), in collaboration with the United States Department of Agriculture, initiated a large-scale screening program for antitumor agents derived from plants. In addition to pure synthetic, or semisynthetic compounds, more than 100,000 compounds have been screened during the past 50 years. Surprisingly, only 7 plant-derived anticancer drugs have received Food and Drug Administration (FDA) approval for clinical application. The major sources of anticancer agents used in clinical practice for the time being are:

- Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host.
- Natural product.
- Derived from a natural product and usually a semisynthetic modification.
- Totally synthetic drug, often found by random screening/modification of an existing agent.
- Made by total synthesis, but the pharmacophore is/was from a natural product.
- Vaccine.
- Natural product mimic (subcategory).

Their percentage in each category cited above in shown in Table 1. Over the time frame from around the 1940s to date, of the 155 small molecules, 70% are other than "S" synthetic, with 47% actually being either natural products or directly derived therefrom [4].

On the other hand, vegetables and fruit are also excellent sources of cancer-preventive substances. Intervention to slow down, arrest or reverse the process of carcinogenesis by the use of either natural or synthetic substances individually or in combination therapy has emerged as a promising and pragmatic medical approach to reduce cancer risk. Interdisciplinary research endeavors are now solely directed at understanding the molecular mechanisms involved in chemoprevention. Completion of the human genome sequence and the advent of DNA microarrays using cDNAs have also enhanced the detection and identification of hundreds of differentially expressed genes in response to anticancer drugs or chemopreventive agents. Epidemiological and experimental evidence emphasize that specific compounds may positively inhibit carcinogenesis at various sites, including the oral cavity, esophagus, stomach, colon/rectum, lung, breast, and prostate, but at the same time, another compelling body of evidence, together with the data from animal and *in vitro* studies, strongly supports the relationship between dietary constituents and the risk of cancer development [5]. The NCI has identified about 35 plant-based foods that possess cancer-preventive properties. Numerous cell-culture and animal model studies have been conducted to evaluate the ability of specific edible plants to prevent cancer. The most exciting findings have been achieved with antioxidant vitamins and their precursors, which are found in dark, leafy green vegetables and yellow/orange fruit and vegetables.

Recently, the focus and emphasis have shifted to the non-nutritive phytochemicals. The NCI has determined in laboratory studies that more than 1,000 different phytochemicals possess cancer-preventive activity. It is estimated that there could be more than 100 different phytochemicals in just a single serving of vegetables.

The present short review deals with a number of recent developments in the field of natural products in oncotherapy, including currently used agents, novel products from microorganisms, marine flora, extracts and promising chemopreventing agents from nature.

Table 1. Sources of anticancer therapy

Categories	*Use in chemotherapy (%)*
Totally synthetic drug	30
Derived from natural product	23
Natural product	5
Biological	14
Vaccine	4
Synthetic (pharmacophore from natural product)	4
Totally synthetic/Natural product mimic	10
Synthetic/Natural product mimic	10

Anticancer agents

Recently approved anticancer agents

Since the late 1990s and the rapid expansion of monoclonal antibodies and synthetic protein kinase inhibitors in oncology, anticancer natural products fell out of fashion with the pharmaceutical industry. But in 2007 with the approval of 3 new drugs derived from natural products, the emergence of promising antitumor compounds from microorganisms (e.g. *alvespimycin* etc) and the growing importance of new formulations of known natural product-derived drugs (nanoparticle formulations, oral forms), a new wave for natural products in oncology is wittnessed. The recent approval of the microtubule-targeted epothilone derivative *ixabepi-*

lone (Ixempra®), the DNA-alkylating marine alkaloid *trabectedin* (Yondelis®) and the inhibitor of mTOR protein kinase *temsirolimus* (Torisel®) is quite emphatic of the field evolution, illustrating also the increasing importance of microbial sources [6]. At the same period, a novel onco-pharmacological universe was discovered, with the use of targeted therapeutics made of receptor-specific small molecules such *imatinib* (Gleevec®), or large ones like *rituximab* (Mabthera®). At this stage, the search for natural products in oncology declined and there was hope to envisage rapidly a personalized treatment of cancer with rationally designed magic bullets, silico- or omico-controlled. Patients suffering from chronic myeloid leukaemia have now a good probability of long-term survival, thanks to the discovery of specific tyrosine kinase inhibitors like *imatinib*, *dasatinib* (Sprycel®) or *nilotinib* (Tasigna®).On the contrary, the therapeutic options for patients with advanced melanoma remain quite limited and survival is still extremely low. The activity of *dacarbazine* (Deticene®) against metastatic melanoma was first noticed in the early 1970s [7] and 36 years later, this product remains a standard. There is a strong need for novel anticancer drugs effective against solid tumors, especially at advanced stages of disease. The need is large and urgent for nearly all solid tumors. Just one example: every 3.5min someone is diagnosed with colorectal cancer (CRC); every 9 min someone dies from CRC; and every 5sec someone who should be screened for CRC is not [8].

Natural products in cancer chemotherapy

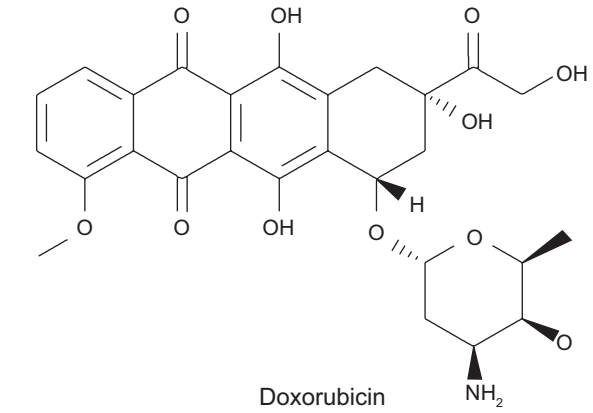
Well-known molecules continue to contribute considerably to cancer chemotherapy. The anthracyclines such as *doxorubicin* (Figure 1), *epirubicin* and *daunorubicin* are some good examples of this kind. This is especially the case for *doxorubicin* (Adriamycin®), extensively used for the treatment of breast cancer, despite the risk of cardiotoxicity particularly in patients with underlying cardiac problems or the elderly. The liposome-encapsulated form improves doxorubicin penetration into tumors and decreases drug clearance, thereby increasing the duration of the therapeutic effect. Pharmacokinetic studies have indeed revealed that the liposomal form results in a longer half-life with less free drug available for tissue distribution than conventional doxorubicin. This liposomal formulation of doxorubicin reduces toxicity, specifically the cardiac effects. This drug is also frequently administered with monoclonal antibodies, with *trastuzumab* (Herceptin®) for breast cancer, and with *rituximab* for lymphoma, for example. In the early seventies there appeared the first clinical reports on the use of *doxorubicin* in the treatment of Hodgkin's disease, leukaemia, breast, lung and cervical cancers. Nevertheless this bacterial product qualified in 1974 as a new drug [9], remains one of the most important molecule of the anticancer armamentarium. The situation is comparable with *mitomycin C,* discovered in the mid-1950s [10], used clinically in the early 1960s and still prescribed nowadays for lung, gastric, colorectal and pancreatic cancers. This antibiotic, originally isolated from *Streptomyces caespitosus*, is a bioreductive drug that requires metabolic activation by cellular reductases, such as NAD(P)H: quinone oxidoreductase-1 (NQO1). It is widely used systemically for the treatment of malignancies, and has gained popularity as topical adjunctive therapy in ocular and adnexal surgery over the past two decades. Similar examples such *bleomycin* [6] (Figure 1) and *actinomycin* [6], old antitumor antibiotics, are still on the shelves of clinical oncologists. A parallel situation can be established with drugs derived from plants.

Paclitaxel (Figure 1), a milestone in late chemotherapy, was originally isolated from the bark of *Taxus brevifolia* in 1966 by Wani and Wall, and in 1971 its structure was confirmed [11]. In 1979, Schiff and Horwitz made the surprising discovery that paclitaxel stimulated microtubule polymerization [12]. Paclitaxel was initially approved by the FDA for treatment of advanced ovarian cancer in 1992 and subsequently endorsed for the treatment of metastatic breast cancer in 1994 [13]. *Docetaxel,* [13] a closely related semisynthetic analog of paclitaxel, was also approved by the FDA in 1996 for the treatment of anthracycline-refractory advanced breast cancer and is now also used to treat lung cancer.

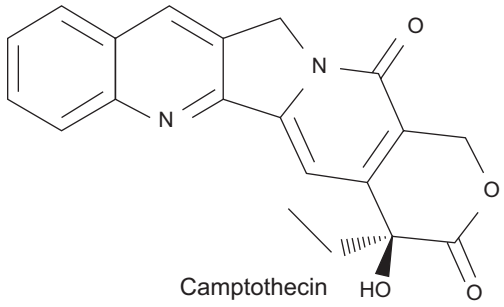
Camptothecin (Figure 1) is mainly obtained from the happy tree (*Camptotheca)*, and was also discovered by Wall and Wani during systematic screening of natural products for anticancer drugs [14]. Two camptothecin analogs, topotecan and irinotecan, have been approved by the FDA and are currently used as chemotherapeutics [15]. Camptothecin binds to and stabilizes the covalent topoisomerase/DNA complex, forming a ternary complex [16]. This prevents DNA re-ligation, causing DNA damage and subsequent apoptosis.

Etoposide phosphate (Eposin, Etopophos, Vepesid and VP-16) is used to treat malignancies such as Ewing's sarcoma, lung cancers, testicular cancers, lymphomas, non-lymphocytic leukemias and glioblastoma multiforme and is derived from *podophyllotoxin*, an inhibitor of the enzyme topoisomerase II [17,18]. It is obtained from *Podophyllum peltatum* and *Podophyllum hexandrum* [19].

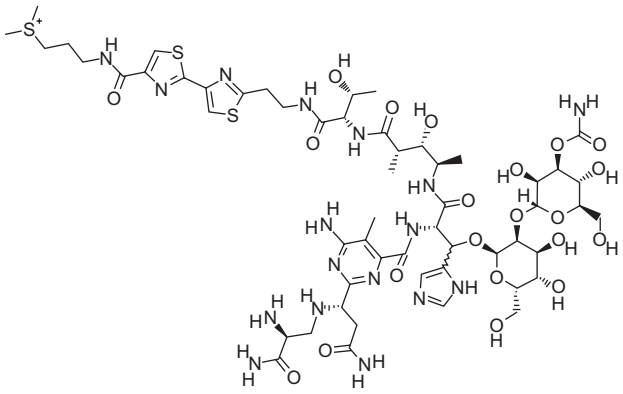
The source of *vinblastine, vincristine* and *vindesine* (Figure 1) is the Madagascar periwinkle, *Catharanthus roseus*. *Vinorelbine* (Navelbine®) (Figure 1), the major semisynthetic tubulin-binding vinca alkaloid, was first



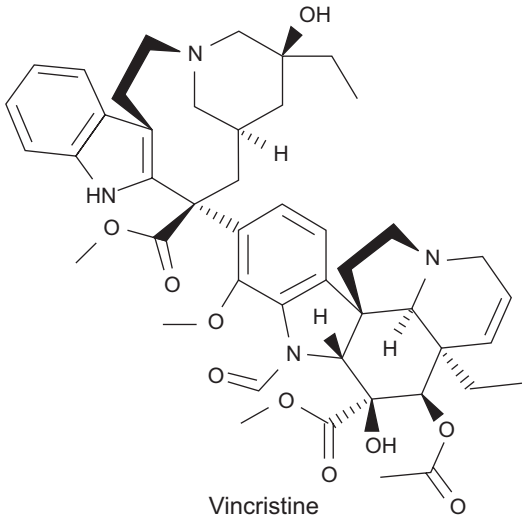
Doxorubicin



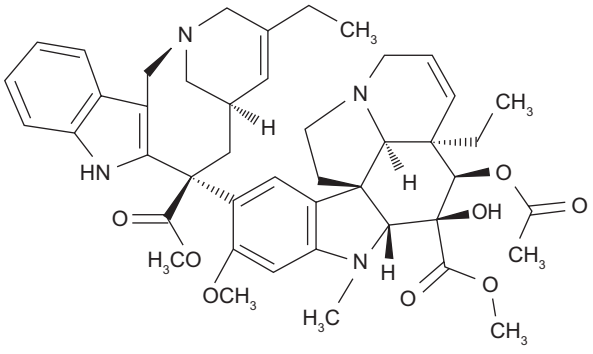
Camptothecin



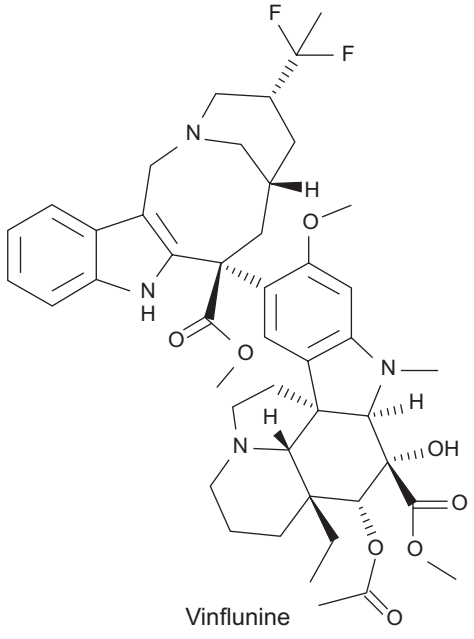
Bleomycin



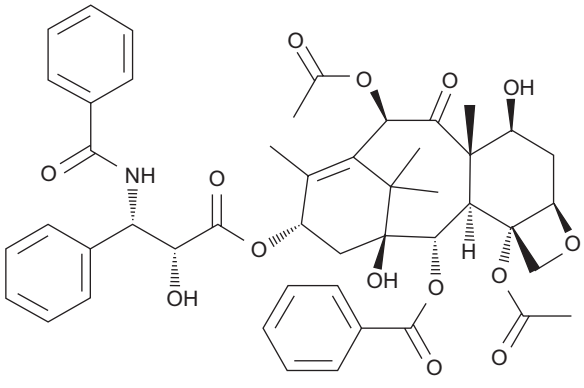
Vincristine



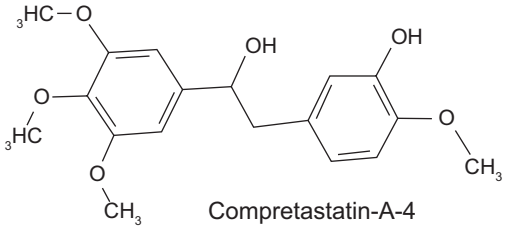
Vinorelbine



Vinflunine



Paclitaxel



Compretastatin-A-4

Figure 1. Chemical structures of natural anticancer agents.

approved in Europe in 1989 and in the USA in 1994 for the treatment of non-small cell lung cancer (NSCLC), then of advanced breast cancer [20]. The related family of *Vinca* alkaloids primarily targets tubulin and microtubules; at high concentrations, these alkaloids depolymerize microtubules and destroy the mitotic spindles, leaving the dividing cancer cells with condensed chromosomes and blocked in mitosis [21].

New promising natural products

Several other promising natural drug candidates are presently in the course of clinical trials. These include: *vinflunine* (Javlor®) (Figure 1), the latest semisynthetic vinca alkaloid with promising activity for the treatment of bladder, breast and non-small cell lung cancers [22,23], *amrubicin,* a third-generation synthetic anthracycline targeting topoisomerase II, which recently received FDA fast track designation for the treatment of small cell lung cancer (SCLC) after first-line chemotherapy [24], and *alvespimycin* (KOS-1022, 17-DMAG, from *S. hygroscopicus*), an orally active heat-shock protein (Hsp) 90 inhibitor derived from 17-allylaminogeldanamycin [25].

Anticancer agents from microorganisms

Microorganisms are the most attractive source for the production of medically useful secondary metabolites. Actinomycetes have been one of the most investigated groups during the past 50 years. Filamentous fungi have been largely studied too. But even if these two groups have already received a major attention, there is still room for the discovery of highly potent anticancer natural product in these families. It is estimated that the number of antibiotics characterized to date represents less than 5% of the total. In the next 10 years, this percentage should be increased significantly with the improvement of cultivation methods of prokaryotic organisms and potentially the growing exploitation of metagenomic approaches for uncultivable microorganisms. A number of pharmaceuticals carry on with the development of plant natural products e.g. the *2''-oxovoruscharin* derivative UNBS1450 semisynthesized from a cardenolide extracted from *Calotropis procera* [26], the semisynthetic *triptolide* derivative from the Chinese medicinal plant *Tripterygium wilfordii* or the microtubule-depolymerizing vascular-disrupting agent *combretastatin-A4* phosphate (Zybrestat®) (Figure 1) [27].

Anticancer agents from marine macroorganisms

This is another great source of secondary metabolites, which have also lost some popularity in the pharmaceutical industry in recent years, mainly due to the difficulty of large-scale supply. Marine macroorganisms are difficult to collect in large scale. Moreover, the compound of interest initially found in the macroorganism derives in fact from a symbiotic microorganism. A typical example is that of the *dolastatins,* first isolated from the mollusc *Dolabella auricularia* and later found to be produced by cyanobacteria [28]. The same case is *ecteinascidin, discodermolide, halichondrin B* and *bryostatin 1*. The histone deacetylase inhibitor depsipeptide *romidepsin* (FK228) has received a fast-track status by the FDA in October 2004 as monotherapy for the treatment of patients with refractory cutaneous T-cell lymphoma, i.e. 10 years after its first isolation from *Chromobacterium violaceum* No.968 [29, 30]. *ET-743*, a significant agent in the development of marine-derived anticancer drugs, was extracted from the Caribbean tunicate *Ecteinascidia turbinate*. A series of alkaloids was identified [31,32] in 1990, and the most abundant active component, *ET-743,* and its *N*-dimethyl analogue *ET-729* have similar potency. Subsequently, *ET-743* was selected for further development, mainly as a result of its greater abundance in *E. turbinata*.

Extract screenings

In addition to pure compounds, natural extracts are very often considered as a promising source. Out of the plethora cases, one example worth mentioning is the antitumor activity of *Kanglaite injection*, a micro-emulsion prepared from an extract of the Chinese plant *Semen coicis*. Kanglaite was the first drug derived from a traditional Chinese herbal remedy to go into clinical trials in the USA [33]. The design of highly robust and sensitive high throughput screening (HTS) assays is a key element. For example, the specific design of a HTS procedure for the discovery of naturally occurring proteasome inhibitors [34] allowed us to identify original molecules from a plants' collection, such as *physalin A* from the tropical herb *Physalis angulata* and *Witheringia hunzikeri* [35,36]. The most popular approach to identify novel natural products in oncology refers to cell cytotoxicity measurements [37-41]. Cell-based assays are routinely used to evaluate the cytotoxicity of standardized extracts (or pure natural products) against murine or human cancer cells cultivated *in vitro*. The use of sophisticated models, more stringent and of a higher predictive value for clinical efficacy are favored. An interesting approach consists to use multicellular tumor spheroid models which are of intermediate complexity between *in vivo* tumors and *in vitro* monolayer cultures. Multicellular spheroids can be generated in 96-well

plates format for HTS, from a variety of tumor cell lineages [42,43].

Proteasome inhibitors

The ubiquitin-proteasome pathway is thought to play a critical role in the degradation of proteins involved in cell cycle control and tumor growth. A complex enzyme cascade first marks proteins destined for degradation by the covalent addition of multiple molecules of ubiquitin. The proteasome hydrolyzes only those proteins that have been marked for destruction by this ubiquitin enzyme cascade. The 20S proteasome, the core component of the proteasome complex, is composed of 4 subunits forming a hollow cylinder that has multiple proteolytic sites on the interior wall [44].

The drug *bortezomib* (Velcade®) has been approved initially for the treatment of relapsed/refractory multiple myeloma and more recently for the treatment of mantle cell lymphoma. This boronic acid dipeptide is an effective reversible inhibitor of the chymotryptic protease in the 26S proteasome, which blocks activation of nuclear factor κB (NF-kB), resulting in increased apoptosis, decreased angiogenic cytokine production, and inhibition of tumor cell adhesion to stroma [45]. The development of a new generation of proteasome inhibitors in bortezomib-resistant tumors is an active scientific field. The most promising drug in this category is the chlorinated natural product *salinosporamide* from the marine actinomyces *Salinispora tropica*. Unlike bortezomib, which is a reversible inhibitor, salinosporamide covalently binds to the proteasome, resulting in the irreversible inhibition of 20S proteasome activity. Salinosporamide was shown to act synergistically with bortezomib to trigger apoptosis in multiple myeloma cells *in vitro* and *in vivo* in a human plasmacytoma xenograft mouse model [46,47]. This natural product is active orally and has shown efficacy in a range of animal models for both hematological malignancies and solid tumors and is currently undergoing phase I clinical trials. Another novel promising irreversible inhibitor of the proteasome is *carfilzomib*, derived from the actinomyces' metabolite epoxomycin, which inhibits proliferation and activates apoptosis in patient-derived multiple myeloma cells. This peptidyl inhibitor shows increased efficacy compared with bortezomib and is active against cell samples from patients with clinical bortezomib resistance [48]. Carfilzomib is currently in Phase 2 clinical trials in patients with relapsed or refractory multiple myeloma and in Phase 1 in lymphoma.

Other microbial products targeting the proteasome have been identified, such as the *cinnabaramides* isolated from a terrestrial streptomyces, *belactosines A and C* from *Streptomyces* spp., the cyclic peptide TMC-95 from the fungus *Apiospora montagnei*, *fellutamide B* from *Penicillium fellutanum*, and *syringolin A* secreted in plants by a strain of *Pseudomonas syringae* [49], which is a pseudo-peptide virulence factor that irreversibly inhibits all three catalytic activities of eukaryotic proteasomes, via a novel mechanism of covalent binding to the catalytic subunits [50]. Proteasome inhibitors have also been identified from plant extracts. This is the case for *celastrol* from the Chinese medicinal plant *Tripterygium wilfordii*, *withaferin A* from the medicinal plant "Indian Winter Cherry", *pristimerin* from plants of the Celastraceae and Hippocrateaceae families. *Topotecan, irinotecan*, and newer compounds in clinical trials such as *gimatecan* and *diflomotecan,* all exploit the same property of the enzyme, DNA cleavage which they promote through stabilization of the DNA-topoisomerase I covalent complex which is normally transient [6].

Chemopreventing agents

Cancer results from a multistage, multi-mechanism carcinogenesis process that involves mutagenic, cell death and epigenetic mechanisms, during the three distinguishable but closely allied stages: initiation, promotion, and progression. Because reducing the initiation phase to a zero level is impossible, the most effective intervention would be at the promotion phase to eliminate premalignant cells before they become malignant [51].

It takes several years for the normal cells to transform into malignant ones. Therefore, the concept of delaying or preventing this transformation remains a viable and attainable goal for the future [52].

The mechanistic insight into chemoprevention further includes induction of cell cycle arrest and apoptosis or inhibition of signal transduction pathways mainly the mitogen-activated protein kinases (MAPK), protein kinases C (PKC), phosphoinositide 3-kinase (PI3K), glycogen synthase kinase (GSK) which leads to abnormal cyclooxygenase-2 (COX-2), activator protein-1 (AP-1), NF-kB and c-myc expression. Effectiveness of chemopreventive agents reflects their ability to counteract certain upstream signals that leads to genotoxic damage, redox imbalances and other forms of cellular stress. Targeting malfunctioning molecules along the disrupted signal transduction pathway in cancer represents a rational strategy in chemoprevention. NF-kB and AP-1 provide mechanistic links between inflammation and cancer, and moreover regulate tumor angiogenesis and invasiveness, indicating that signaling pathways that mediate their activation provide at-

tractive targets for new chemotherapeutic approaches. Thus cell signaling cascades and their interacting factors have become important targets of chemoprevention and phenolic phytochemicals and plant extracts seem to be promising in this endeavor [53]. An ideal chemopreventive agent should have: 1) little or no toxicity; 2) high efficacy in multiple sites; 3) capability of oral consumption; 4) known mechanisms of action; 5) low cost, and human acceptance. A variety of grains, cereals, nuts, soy products, olives, beverages such as tea and coffee, and spices including turmeric, garlic, ginger, black pepper, cumin and caraway confer a protective effect against cancer [54]. In particular, natural products consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids and nitrogen containing as well as organosulfur compounds, which have been shown to suppress early and late stages of carcinogenesis [55].

Recently, a bioactive triterpene, *lupeol* (Figure 2), commonly found in fruits like fig, mango, etc, has attracted interest in the context of chemoprevention attributable in large part to its antioxidant [56], apoptosis-inducing and antiproliferative anti-mutagenic, anti-inflammatory [57] properties, as well as its efficacy in inhibition of *in vivo* and *in vitro* cancer growth. Triterpenes represent a varied class of natural products, which occur commonly and are found in fruits, vegetables and other parts of several medicinal plants e.g. *Arbutus unedo, Tipuana tipu,* etc [58,59]. The last 15 years have seen tremendous efforts by researchers worldwide to develop this wonderful molecule for its clinical use for the treatment of a variety of disorders. These studies also provide insight into the mechanism of action of *lupeol* and suggest that it is a multi-target agent with immense anti-inflammatory potential targeting key molecular pathways which involve NF-kB, cFLIP, Fas, Kras, phosphatidylinositol-3-kinase (PI3 K)/Akt and Wnt/β-catenin in a variety of cells. It is noteworthy that *lupeol* at its effec-

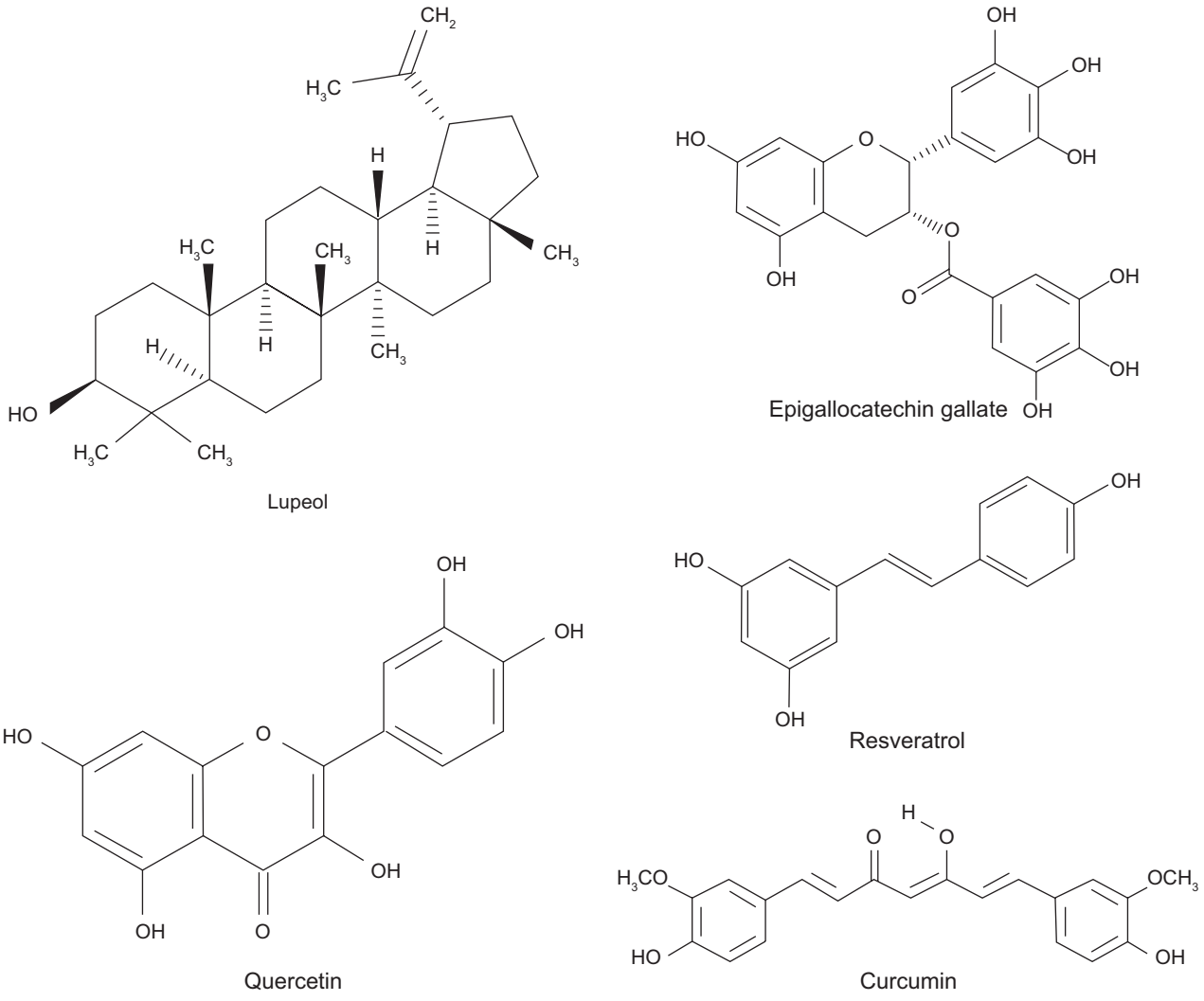


Figure 2. Chemical structures of natural chemopreventing agents.

tive therapeutic doses exhibits no toxicity to normal cells and tissues [60]. NF-kB, a transcription factor first discovered in 1986, is now known to be closely connected to the process of tumorigenesis based on a multiplicity of evidence. NF-kB is activated in response to tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli that account for as much as 95% of all cancers. NF-kB: a) regulates the expression of most anti-apoptotic gene products associated with the survival of the tumor; b) regulates the gene products linked with proliferation of tumors; c) controls the expression of gene products linked with invasion, angiogenesis, and metastasis of cancer. While most carcinogens activate NF-kB, most chemopreventive agents suppress its activation. These observations suggest that NF-kB is intimately intertwined with cancer growth and metastasis.

AP1 is another transcription factor that regulates expression of genes that are involved in cellular adaptation, differentiation and proliferation. Functional activation of AP1 is associated with malignant transformation as well as tumor promotion [61-66].

Phytochemicals targeting NF-kB and AP1

Curcumin (Figure 2), a spice widely used in Indian cuisine, has been identified to show considerable anti-tumor effects. It is a yellow pigment that is present in the rhizome of turmeric (*Curcuma longa* L.) and related species and is one of the most extensively investigated phytochemicals, with regard to chemopreventive potential.

Since the first article referring to the use of *curcumin* to treat human disease was published in 1937, more than 2,600 research studies using *curcumin* or turmeric have been published in English language journals. The mechanisms implicated in the inhibition of tumorigenesis by *curcumin* are diverse and appear to involve a combination of antiinflammatory, antioxidant, immunomodulatory, proapoptotic, and antiangiogenic properties *via* pleiotropic effects on genes and cell-signaling pathways at multiple levels. The potentially adverse sequelae of *curcumin's* effects on proapoptotic genes, particularly *p53*, represent a cause for current debate. When *curcumin* is combined with some cytotoxic drugs or certain other diet-derived polyphenols, synergistic effects have been demonstrated [67].

A late finding is that *curcumin* binds directly to and activates VDR (the nuclear vitamin D receptor), inducing the VDR target genes CYP3A4, CYP24, p21 and TRPV6 [68]. Despite our increasing knowledge on this interesting substance there still remain many unknown effects that deserve intense investigation [69].

Gingerol, a phenolic substance that is responsible for the spicy taste of ginger (*Zingiber officinale*) was reported to inhibit tumor promotion and PMA-induced ornithine decarboxylase (ODC) activity and TNF-production in mouse skin [70].

Capsaicin, a pungent component of hot chilli pepper (*Capsicum annuum* L.) has been suspected to act as a carcinogen or a co-carcinogen in experimental animals because of its irritant properties, but other studies indicate that this compound has chemopreventive and chemoprotective effects [71].

Epigallocatechin gallate (EGCG, Figure 2) is an antioxidant and chemopreventive polyphenol that is found in green tea. It has been shown to suppress malignant transformation in a PMA-stimulated mouse epidermal JB6 cell line, which seemed to be mediated by blocking activation of Ap1 [72].

Genistein, a soy-derived isoflavone, is believed to contribute to the putative breast- and prostate cancer preventive activity of soya. *Genistein* inhibited PMA-induced AP1 activity, expression of c-FOS and ERK activity in certain human mammary cell lines. *Genistein* treatment abrogated NF-kB DNA binding in human hepatocarcinoma cells stimulated with hepatocyte growth factor [73].

Resveratrol (3,4′,5-trihydroxy-*trans*stilbene; Figure 2) is a phytoalexin that is present in grapes (*Vitis vinifera*) and a key antioxidant ingredient of red wine. It is believed to be responsible for the so-called "French paradox", in which consumption of red wine has been shown to reduce the mortality rates from cardiovascular diseases and certain cancers. *Resveratrol* treatment inhibited PMA-induced COX2 expression and catalytic activity, via the cyclic-AMP response element (CRE) in human mammary epithelial cells [74,75]. It also inhibited PKC activation, AP1 transcriptional activity and the induction of COX2-promoter activity in PMA-treated cells. *Resveratrol* induced apoptosis and reduced the constitutive activation of NF-kB in both rat and human pancreatic carcinoma cell lines [76].

Of particular interest is that *resveratrol* is capable of causing DNA breakage in cells such as human lymphocytes. Such cellular DNA breakage is inhibited by copper specific chelators but not by iron and zinc chelating agents [77].

Miscellaneous phytochemicals

In addition to the aforementioned phytochemicals, *quercetin* (Figure 2), a flavonoid which is ubiquitously distributed in edible plant foods, *caffeic acid phenethyl ester, sulphoraphane, silymarin, apigenin, emodin* and *anethole* have also been reported to suppress the activa-

tion of NF-kB and AP1, which might contribute to their chemopreventive and/or cytostatic effects [78].

Phytochemicals that activate NRF

Exposure of HepG2 cells to the green tea extract induces expression of phase II detoxifying enzymes through the antioxidant responsive element (ARE) [79]. This upregulation was accompanied by activation of ERK2 and JNK1, as well as immediate early genes c-*JUN* and c-*FOS*. Subsequent studies have shown that EGCG transcriptionally activated the phase II enzyme gene expression in HepG2 cells, as determined by the ARE reporter-gene assay [80].

NRF-KEAP1 complex

Another important approach to chemoprevention is to block the DNA damage caused by carcinogenic insult, the initiation stage of carcinogenesis.

The phase II enzyme induction system is an important component of the cellular stress response in which a diverse array of electrophilic and oxidative toxicants can be removed from the cell before they are able to damage the DNA. Antioxidants exert their protective effects not only by scavenging reactive oxygen species (ROS), but also by inducing *de novo* expression of genes that encode detoxifying/defensive proteins, including phase II enzymes. Many xenobiotics activate stress-response genes in a manner similar to that achieved by antioxidants. These genes encode enzymes such as glutathione peroxidase, gamma-glutamylcysteine synthetase, GST, NQO and heme oxygenase-1. The 5′-flanking regions of these genes contain a common *cis*-element, known as ARE. Many basic leucine zipper (bZIP) transcription factors, including NRF, JUN, FOS, FRA, MAF and AH receptor, bind to these ARE sequences and modulate the expression of some of the aforementioned stress-response genes [81].

Phytochemicals that target β-catenin

Several dietary phytochemicals have been shown to downregulate the β-catenin-mediated signaling pathway as part of their molecular mechanism of chemoprevention. *Curcumin* and CAPE (caffeic acid phenethyl ester) inhibited tumorigenesis and decreased β-catenin expression in the multiple intestinal neoplasia (Min/+) mouse model [82]. Moreover, *curcumin* reduced the cellular levels of β-catenin through caspase-mediated cleavage of the protein [83]. Downregulation of β-catenin expression by *resveratrol* was observed in a human colon cancer cell line [84].

Expression of a β-catenin–TCF4-binding reporter construct was reduced in HEK293 cells by EGCG (epigallocatechin-3-gallate) [85]. Indole-3-carbinol altered the pattern of β-catenin mutation in chemically- induced rat colon tumors [86], inhibited adhesion, migration and invasion of cultured human breast carcinoma cells, and upregulated E-cadherin and β-catenin [87]. A similar effect was observed with tangeretin from citrus [88]. COX inhibitors have also been found to suppress β-catenin signaling and β-catenin-TCF/LEF transcriptional activity [89-91].

Omega-3 polyunsaturated fatty acids

The dietary omega-3 polyunsaturated fatty acids (PUFAs) can regulate the expression of EZH2 in breast cancer cells.

The polycomb group (PcG) protein, enhancer of Zeste Homologue 2 (EZH2), is overexpressed in several human malignancies including breast cancer. Aberrant expression of EZH2 has been associated with metastasis and poor prognosis in cancer patients. The treatment of breast cancer cells with omega-3 PUFAs, but not omega-6 PUFAs, led to downregulation of EZH2. Studies using the proteasome inhibitor MG132 suggested that omega-3 PUFAs induce degradation of the PcG protein EZH2 through post-translational mechanisms. Furthermore, downregulation of EZH2 by omega-3 PUFAs was accompanied by a decrease in histone 3 lysine 27 trimethylation (H3K27me3) activity of EZH2, and upregulation of E-cadherin and insulin-like growth factor binding protein 3 (IGFBP3), which are known targets of EZH2. Treatment with omega-3 PUFAs also led to decrease in invasion of breast cancer cells, an oncogenic phenotype that is known to be associated with EZH2 [92].

Conclusions

Natural products have been an important source of chemotherapeutics for the past 40 years. Development of naturally derived anticancer drugs, therefore, is crucial, and isolation of novel compounds has become an important part of cancer research. Most anticancer drugs have been discovered through random screening of organism collections, but our improved understanding of many of the molecular details of carcinogenesis and evolution makes it possible to develop more efficient strategies. Plant and organism species may be selected on the basis of potentially useful phytochemical composition by consulting ethnopharmacological, chemosystematic, and ecological information. Additionally,

semisynthesis of new compounds by molecular modification, including combinatorial and computational chemistry, could generate analogues with higher activity and fewer side effects. On the other hand conjugation of toxic natural products to monoclonal antibodies or polymeric carriers can lead to more efficacious targeted therapies. In achieving more desirable results, since less than 15% of higher plants have been systematically investigated, the natural products research towards chemotherapy needs multi scientific collaboration and further support in pharmaceutical companies. In close relation to chemotherapy, chemoprevention enforced by edible phytochemicals is now considered to be an inexpensive, readily applicable, acceptable and accessible approach to cancer control and management. Despite significant advances in our understanding of multistage carcinogenesis, little is known about the mechanism of action of most chemopreventive agents. The chemopreventive effects that most dietary phytochemicals exert are likely to be the sum of several distinct mechanisms. Both pharmacokinetic properties and bioavailability are key problems in investigating the dietary prevention of cancer. With the advances in techniques to assess single nucleotide polymorphisms (SNPs), science is now more aware of the specific genes that can directly and indirectly contribute to individual differences in the susceptibility to carcinogenesis. The term "nutragenomics" has been coined, and much attention is being focused on this relatively new area of research.

With healthcare costs being an international key issue today, it would be cost-effective to promote the awareness and consumption of phytochemicals as a cancer-preventive and therapeutic strategy, within the health system.

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