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Natural products as leads to anticancer drugs

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Abstract Throughout history, natural products have afforded a rich source of compounds that have found many applications in the fields of medicine, pharmacy and biology. Within the sphere of cancer, a number of important new commercialised 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 search for improved cytotoxic agents continues to be an important line in the discovery of modern anticancer drugs. The huge structural diversity of natural compounds and their bioactivity potential have meant that several products isolated from plants, marine flora and microorganisms can serve as "lead" compounds for improvement of their therapeutic potential by molecular modification. Additionally, semisynthesis 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. These processes, complemented with high-throughput screening protocols, combinatorial chemistry, computational chemistry and bioinformatics are able to afford compounds that are far more efficient than those currently used in clinical practice. Combinatorial biosynthesis is also applied for the modification of natural microbial products. Likewise, advances in genomics and the advent of biotechnology have improved both the discovery and production of new natural compounds.

Key words Natural lead compound • Anticancer • Camptothecin • Podophyllotoxin • Taxol • Vinblastine

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Cancer and natural products

Natural products have been a rich source of agents of value to medicine. More than half of currently available drugs [1] are natural compounds or are related to them, and in the case of cancer this proportion surpasses 60%. This situation is accompanied by increasing interest from drug companies and institutions devoted to the search for new drugs [2, 3].

Additionally, many new natural compounds of diverse structures, isolated from plant sources [4, 5], have been considered *prototypes*, *leads* or *heads of series* and their later structural modification has afforded compounds with pharmacological activity and extraordinary therapeutic possibilities [6–11].

This area of research, which is continually expanding and is of enormous current interest, explores new natural products coming from different sources, among which the sea could be quoted as an almost infinite source of resources [12–19], with a view to collecting more potent, more selective and less toxic compounds than today's drugs, and hence with better therapeutic indices. Currently, more than 30 compounds of natural origin are in different phases of clinical study for the treatment of different types of cancer. Of importance are ixabepilone (epothilone B from *Soragium cellulosum*), romidepsin (depsipeptide from *Chromobacterium violaceum*) and the dibenzodiazepine ECO-4601 (from

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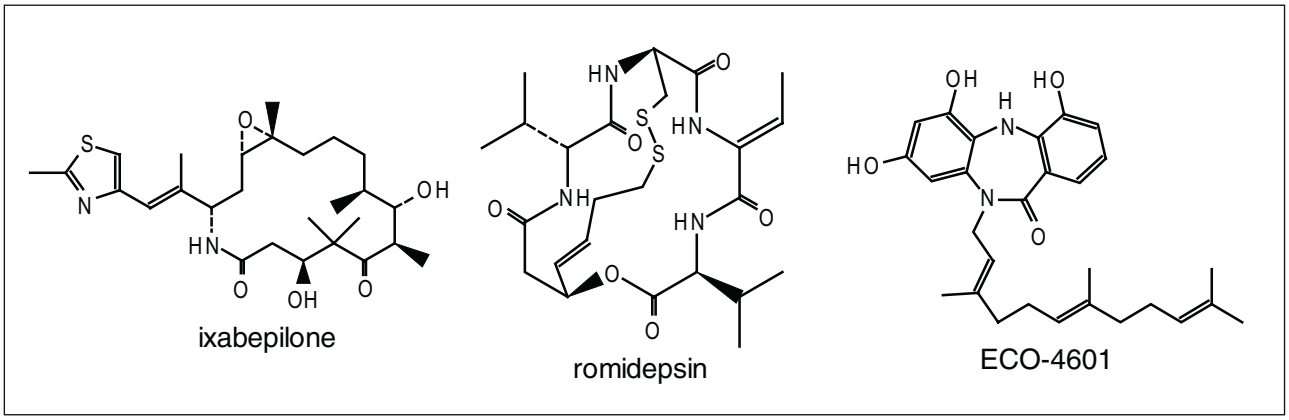

Fig. 1 Natural compounds in different phases of clinical studies

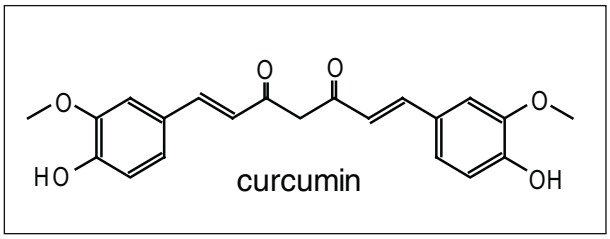

Fig. 2 Curcumin from the dried rhizomes of *Curcuma longa*

Micromonospora sp.), apart from other new natural compounds that in the future may be developed into new drugs or leads, which –through further modifications– could afford more potent, more selective and less toxic compounds than currently available anti-cancer drugs [1, 20] (Fig. 1).

Recently, romidepsin has received the Orphan Drug Designation from the US Food and Drug Administration (FDA) for the treatment of non-Hodgkin T-cell lymphomas. Romidepsin is a novel agent in a new class of anti-cancer drugs, known as histone deacetylase inhibitors [21], and it induces chromatin remodelling, tumour suppressor gene transcription, growth inhibition, apoptosis, differentiation and antitumour activity [22].

Although with a simpler structure than those of the molecules mentioned above, curcumin, a compound in the human food supply, represents a good starting point for drug discovery from a natural product [23]. Curcumin is a phytochemical obtained from the dried rhizomes of *Curcuma longa* and has gained interest due to its anti-oxidant, antiproliferative, antiangiogenic and anti-tumorigenic properties. However, owing to its low potency and poor bioavailability, it has not met with success as a drug. The significant antineoplastic activity of curcumin, along with its low molecular weight and lack of toxicity, makes this molecule a good natural lead compound for the collection of potential chemotherapeutic derivatives or analogues [24–27]. Consequently, a broad variety of curcumin analogues have been prepared. One widely used structural modification truncates the central conjugated beta-diketone in curcumin to the monocarbonyl dienone. A diverse array of the latter compounds exhibit cytotoxicities against an equally diverse set of cancer-related cell lines. Importantly, in rodents these compounds still retain toxicity profiles that are comparable to that of the parent natural product, whereas some analogues exhibit good oral bioavailability and good pharmacokinetics, and evidence has been provided regarding their antiangiogenic activity in cell cultures [23] (Fig. 2).

Molecular modification of lead natural products

Pharmacomodulation is a method used to search for new drugs and consists in taking as the *origin, lead, prototype* or *series head* a chemical substance of suitably established structure and of known biological activity and preparing and testing its structural analogues. The main aims of pharmacomodulation are to establish relationships between the structure and pharmacological activity of the compounds and obtain drugs better than the *prototype*. Within the field of natural products, pharmacomodulation has provided important results, as regards improvements in both the activity and the pharmacokinetic properties of drugs.

Natural compounds offer huge structural diversity and in some cases great biological potency [28]. It is thus difficult for chemical synthesis to replace cellular biochemistry as a source of new drugs.

These aspects, together with the enormous biodiversity of the planet (plants, the ocean and microorganisms), in many instances not yet explored, mean that natural compounds could offer promising sources of drugs; indeed, far greater than compounds achievable by synthesis. Nature is continually surprising us with new chemical structures or unusual skeletons, some with powerful cytotoxic properties (e.g. gymnastatin G from

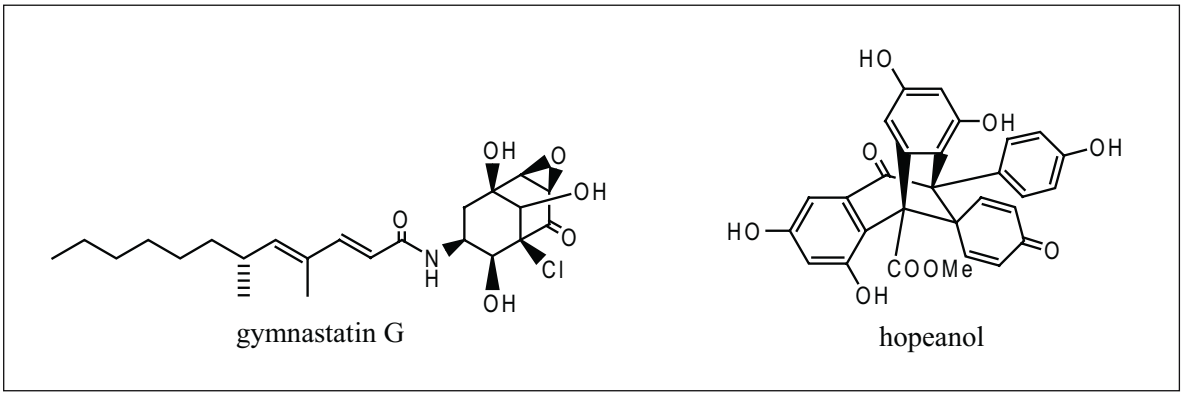

Fig. 3 New chemical structures or unusual skeletons with cytotoxic properties

Gymnascella dankaliensis and hopeanol from *Hopea exalata*) [29]. The sponge-derived fungus *Gymnascella dankaliensis* is the source of several cytostatic metabolites, including gymnastatin G, which has an unusual bicyclo[3.3.1]nononane ring system [30]. The highly cytotoxic hopeanol, from the bark of *H. exalata*, has a new carbon skeleton [31] (Fig. 3).

Currently, there are complementary tools available for structural modification. These are suitable for preparing analogues and uncovering the structure–activity relationships that should allow us to enhance natural compounds, thereby increasing the possibilities of obtaining new drugs. In this sense, the application of combinatorial chemistry [32] allows the generation of libraries [33, 34] of analogous molecules of natural compounds that can be transformed into lead molecules for the preparation of new, more potent and less toxic compounds. Additionally, combinatorial biosynthesis allows metabolic pathways to be manipulated, it then being possible to improve the production of a given natural metabolite [35].

The application of molecular genetic techniques has permitted the manipulation of biosynthetic pathways for the generation of novel lead compounds directed at the new targets arising from genomics projects. The exploitation of structural chemical databases comprising a broad variety of chemotypes, in conjunction with databases on target genes and proteins, should facilitate the creation of new chemical entities through computational molecular modelling for pharmacological evaluation [33, 34, 36].

Some important anticancer natural leads

One example of these leads is podophyllotoxin, a natural cyclolignan with antiviral and antitumour properties. The chemistry explored around this compound has given rise to the introduction in clinical practice of etoposide (and its pro-drug etopophos) and teniposide: drugs that are efficacious against cancers of the lung and colon and against leukaemia, among other antineoplastic properties.

Other examples of natural lead anticancer compounds are molecules such as camptothecin, paclitaxel or vinblastine. These compounds and their derivatives show extraordinary antineoplastic properties, some of them being found among the most widely prescribed chemotherapeutic agents.

Podophyllotoxins: anticancer activity and uses

Cytotoxicity and antiviral activity are the most important features currently underlying our interest in podophyllotoxin and its analogues [37]. Podophyllotoxin is the most abundant lignan isolated from podophyllin, a resin obtained from species of the genera P*odophyllum* (*Berberidaceae*) [38]. Since ancient times, podophyllotoxin has been used for medicinal purposes as a cathartic and antihelminthic agent.

Nevertheless, podophyllotoxin is included in many pharmacopoeias and is used as an antiviral agent in the treatment of *Condyloma acuminatum*, caused by the HPV papilloma virus, and other venereal and perianal warts [39]. Additionally, like other related lignans –deoxypodophyllotoxin, picropodophyllotoxin and peltatins α and β among others– it has proved effective against type I herpes simplex virus and measles [40].

Podophyllotoxin has other uses in dermatology [41] and in the treatment of rheumatoid arthritis [42], and its immunostimulatory activities have been described [43].

Despite this broad variety of pharmacological properties, it was podophyllotoxin's antitumour properties, discovered halfway through the last century, that propitiated an extraordinary arousal of interest in cyclolignans and led podophyllotoxin to become a lead compound in the search for more efficient antineoplastic agents.

Podophyllotoxin is effective in the treatment of Wilms' tumours, different types of genital tumours (carcinoma verrucosus, for example), and in non-Hodgkin and other lymphomas [37] and lung cancer [44, 45] (Fig. 4).

With a view to achieving greater therapeutic efficiency, combination therapies are currently being implemented

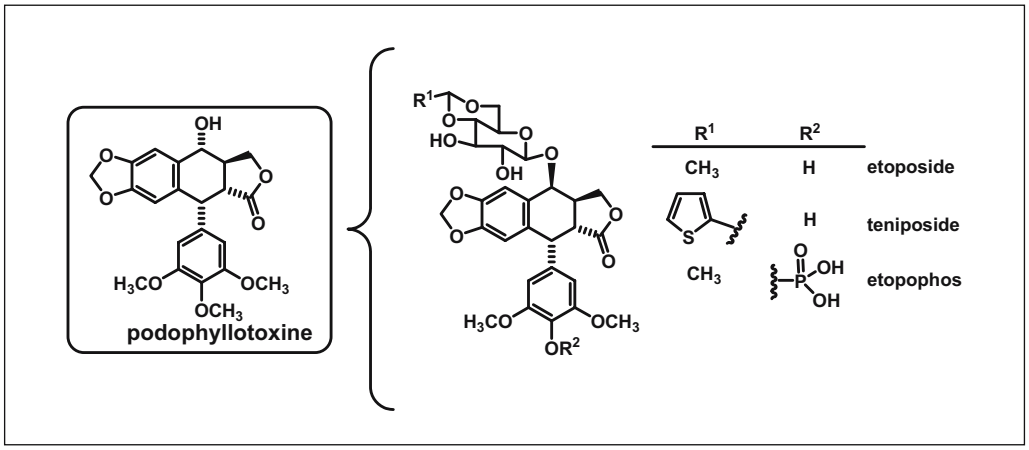

Fig. 4 Podophyllotoxins

with other chemotherapeutic agents or with other techniques useful in the fight against cancer. In this sense, multiple myeloma responds best to homeotherapy with podophyllotoxin and intermittent local administration of methotrexate and systemic polychemotherapy. In combination with cisplatin, podophyllotoxin is effective in treating neuroblastomas [46].

Podophyllotoxin-like lignans inhibit the polymerisation of tubulin, arresting the cell cycle in the metaphase [47–49].

Several studies addressing cyclolignans [50–52] have shown that cyclolignanolides of the podophyllotoxin group might work as alkylating agents of biomolecules through their C-9 methylene, rather than as acylating agents (Fig. 5).

Etoposide, teniposide and etopophos

Three semisynthetic derivatives of the cyclolignan podophyllotoxin –etoposide, teniposide and etopophos– are widely used anticancer drugs and show good clinical effects against several types of neoplasms, including testicular and small-cell lung cancers, lymphoma, leukaemia, Kaposi's sarcoma, etc. [37, 53–56]. However, several limitations, such as myelosuppression, the development of drug resistance and cytotoxicity against normal cells remain to be resolved.

Etoposide-like compounds are potent irreversible inhibitors of DNA topoisomerase II and their action is based on the formation of a nucleic acid-drug-enzyme complex, which induces single- and double-stranded DNA breaks as the initial step in a series of biochemical transformations that eventually lead to cell death [37, 49, 57–61].

In order to overcome the limitations of these compounds and to develop new compounds with better antitumour activity, many structural modifications have been performed on the cyclolignan skeleton.

In this sense, many investigators have focused their research on the design, semisynthesis and synthesis of novel analogues of podophyllotoxin. This has afforded very interesting results, reviewed in a large number of scientific articles [37, 47, 62–77 and references cited therein].

Thus, many new cyclolignans have been prepared by modification of nearly all the rings of the skeleton in the

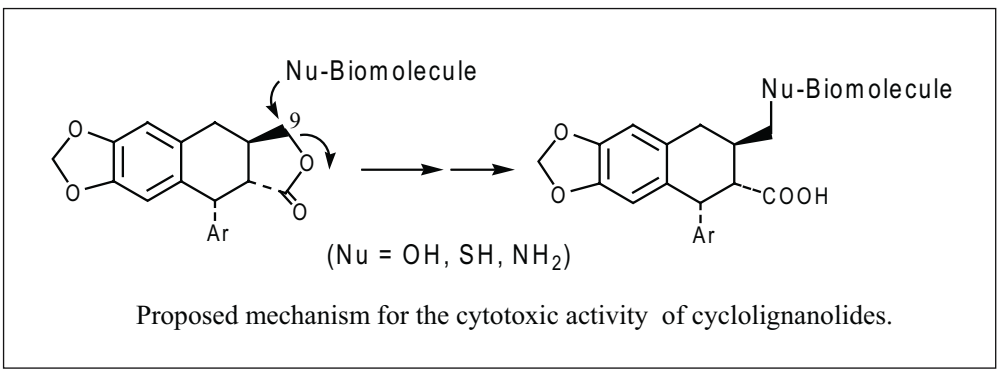

Fig. 5 Action mechanism for cyclolignanolides

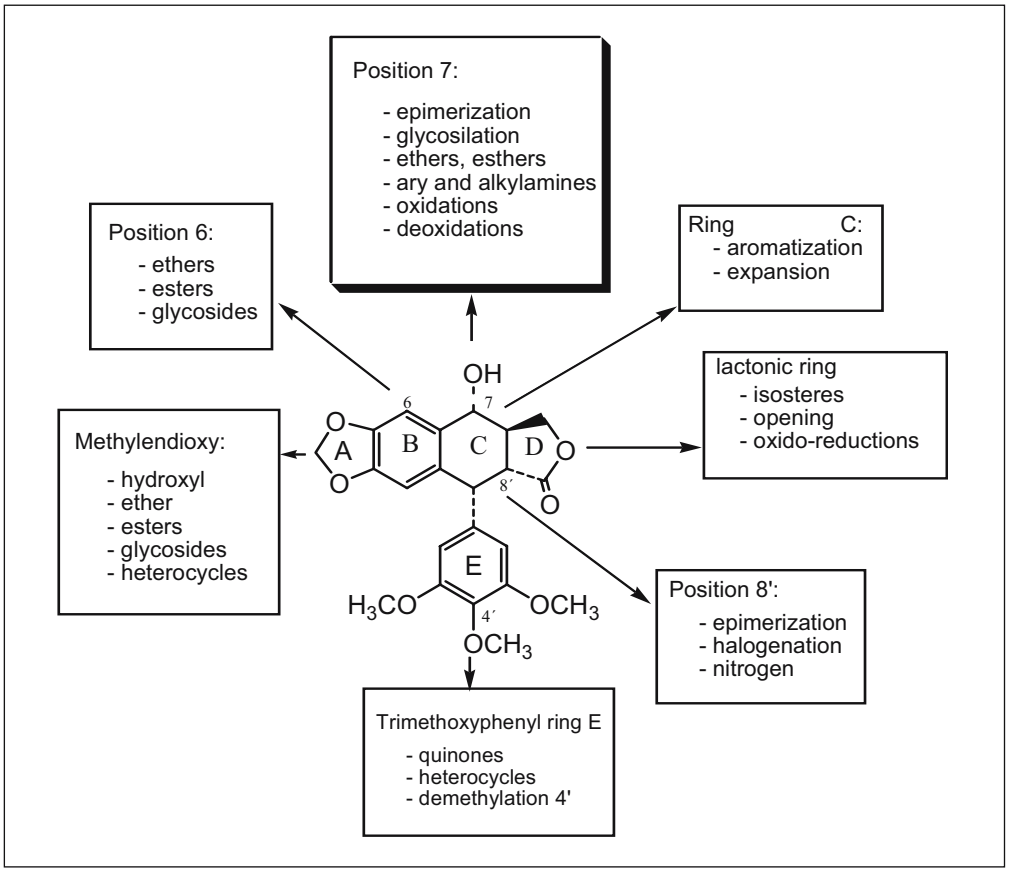

Fig. 6 SAR studies in cyclolignans

search for more potent, less toxic and more selective analogues. Podophyllic aldehyde, a new compound obtained from podophyllotoxin, has become a new lead compound for further chemical modifications, of which the imine derivatives not only maintain the level of cytotoxicity of the parent aldehyde, but also improve selectivity against HT-29 colon carcinoma [78–80].

A summary of the main structural modifications carried out on the different rings and positions of podophyllotoxin can be seen in the following figure (Fig. 6):

Studies on structure–activity relationships carried out to date on a broad variety of the compounds already prepared highlight the importance of such modifications with respect to the mechanism of action of such compounds [51, 57, 69, 70].

Because etoposide and teniposide are drugs widely used in clinical practice and have position 7 substituted, this position in the cyclolignan skeleton is the most modified: 7β-aniline and 7-imidepodophyllotoxin [81], 7β-mono-, di- and trisubstituted aniline-4'-demethylpodophyllotoxin [82], 7-aminoepipodophyllotoxin derivatives, γ-lactone ring-modified 7-aminoetoposide analogues [5, 83], deoxypodophyllotoxin [84], 7β-aminodeoxypodophyllotoxin and 7-amino-4'-demethyldeoxypodophyllotoxin [85], 7-aza-8,8'-didehydropodophyllotoxins [86]. Modification at position 7 also encompasses glycosides such as podophyllotoxin glucosides [87], isopodophyllotoxin glucoside and 4'-demethylpicropodophyllin glucoside [88]. Also (+)-7-acetyl-6-methoxypicropodophyllin, (+)-7-acetylpicropodophyllin [89], 7-β-propenylpodophyllotoxin ethers [90], (–)-7-aza-7-deoxypodophyllotoxin [91–93], 7-imidazol [94], 7-tetrahydropyridine [95] and glycine polymer of podophyllotoxin have been prepared [96].

Camptothecin, topotecan and irinotecan

Camptoteca acuminata is a tree found in Tibet and China, where it is known as the tree of happiness (Xhi Shu). Its main active component is camptothecin, a quinoline alkaloid whose antitumour activity was discovered in 1958 [97, 98]. Camptothecin and its derivatives exhibit the property of inhibiting DNA topoisomerases by stabilising certain intermediate complexes produced during DNA synthesis [49, 57, 59, 61, 74, 99–104]. As DNA replication is prevented, so is cellular proliferation. Camptothecin has been modified chemically [105, 106] to reduce its toxic effects and two of its derivatives have been commercialised: namely, topotecan and irinorecan [107, 108] (Fig. 7).

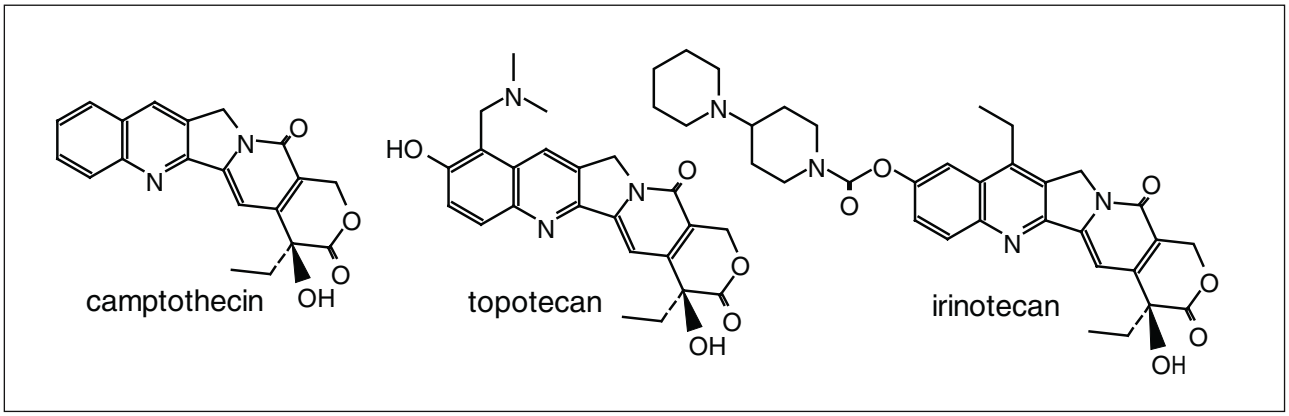

Fig. 7 Camptothecin, toptecan and irinotecan

Topotecan is applied to metastatic ovarian cancer [71] and has efficacy in small-cell lung cancer [109–116]. Irinotecan is a pro-drug of the active metabolite, and it is useful in metastatic colorectal cancer [117, 118] in combination with fluorouracil and oxaliplatin [118–122].

Camptothecin and its analogues act by inhibiting topoisomerase I, a cellular enzyme that maintains the topographic structure of DNA during translation, transcription and mitosis. Topoisomerase I alleviates the coiling strain of the DNA double helix during replication and transcription by transiently breaking one of the chains of the double helix, a DNA-topoisomerase complex being formed, after which it is joined up again. Camptothecin and its derivatives bind to the DNA-topoisomerase complex and prevent this "re-soldering" from taking place. However, for these compounds to show potent cytotoxicity (DNA-topoisomerase complexes are somewhat unstable and they degrade when the drug is removed), DNA synthesis must be initiated. At this moment, when the fork formed by the two DNA strands encounters topoisomerase-irinotecan complexes, a double breakage of the strands occurs, in this case irreversible. Thus, irinotecan and related compounds are highly specific to the S phase of the cell cycle and elicit the arrest of the cell cycle in G2. Accordingly, agents that, like hydroxyurea, inhibit DNA synthesis are able to protect cells against the cytotoxicity of camptothecins [99 and references cited therein].

Vinblastine and vincristine

Vinblastine and vincristine are vinca alkaloids isolated from the pink periwinkle plant *Catharantus rosea* (formerly *Vinca rosea* Linn) [123–125]. This class of alkaloids includes vinorelbine and vindesine, and other indole compounds obtained by simple structural modification of natural leads [126, 127].

Vinca alkaloids have similar structures but show differences both in their activity spectrum and in their toxicity [128, 129]. Vincristine is more effective against non-Hodgkin lymphoma, Hodgkin's disease and paediatric solid tumours than against adult solid tumours. In contrast, vinorelbine is more effective against breast and lung cancer. Vinblastine is used in the treatment of testicular cancer, non-Hodgkin lymphoma, breast cancer, head and neck cancer, cervico-uterine cancer and bladder cancer [130] (Fig. 8).

Vinblastine prevents cancerous cells from undergoing mitosis. It does so by inhibiting the formation of fibres in the achromatic spindle. The fibres of the spindle are responsible for chromosomal alignment and separation during anaphase. Vinblastine blocks the formation of microtubules and binds to the α and β subunits of tubulin in the S phase of the cell cycle; without the appropriate microtubules, cell division is impossible [60]. Like all vinca alkaloids, this drug also affects the division of normal cells, thus explaining several of the undesirable side effects [131, 132].

Paclitaxel (Taxol®) and docetaxel (Taxotere®)

Paclitaxel is a diterpene with a taxane nucleus that was first isolated from the bark of the Western yew *Taxus brevifolia*, a tree native to western North America. Later, it was found in the leaves of several species of *Taxus.* However, the content of paclitaxel in *Taxus* is very low [133–136]. Another source of paclitaxel is semisynthesis from 10-deacetyl-baccatin III, which is available from the leaves of *Taxus baccata*. Total synthesis of paclitaxel has been achieved, but is too complex to be used as a commercial source of the drug [137–145].

Taxol was approved by the US FDA in 1992 for the treatment of drug-refractory metastatic ovarian cancer. It has also shown promising results in clinical trials in lung, breast, and head and neck cancer.

The mechanism of action is unique [146–149]. The taxanes disable the mitotic apparatus by disrupting the normal function of microtubules. They act as microtubu-

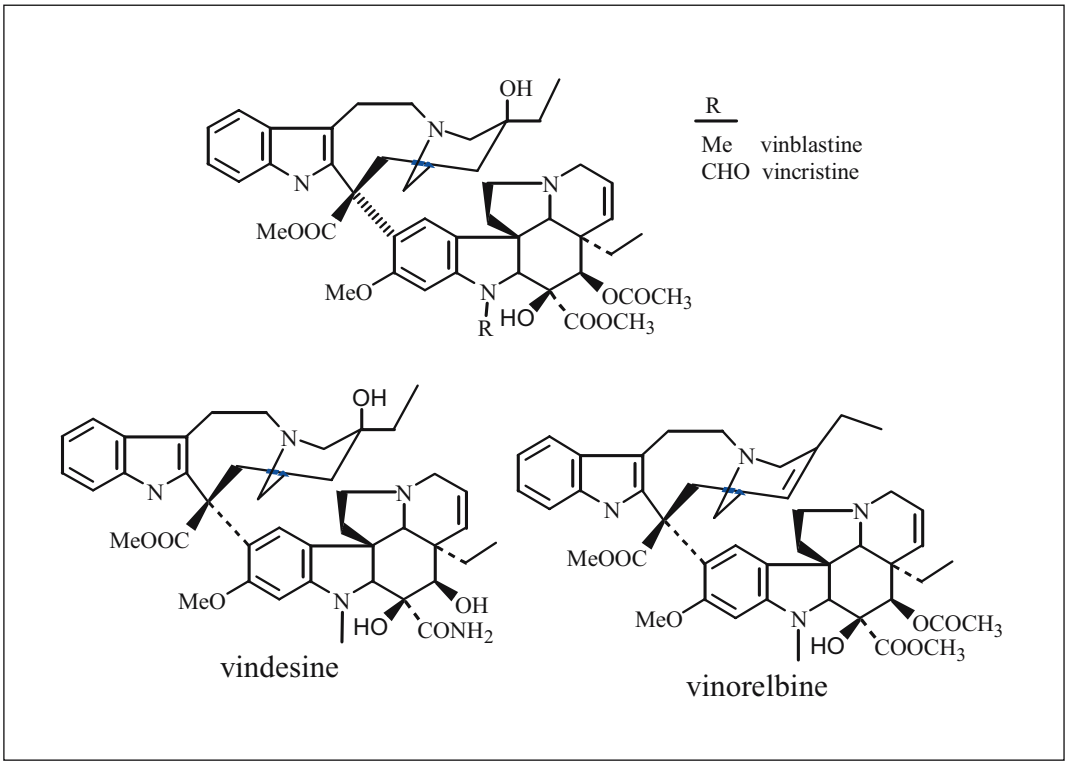

Fig. 8 Vinblatine and related compounds

lin-stabilising agents while the other inhibitors of mitosis such as vinca alkaloids destabilise this process. Whereas vinca alkaloids affect the rates of tubulin polymerisation, the taxanes induce the inhibition of microtubule depolymerisation. Like vinca alkaloids, the mechanism of action of taxanes is dose-dependent [150, 151].

Docetaxel is a semisynthetic analogue of paclitaxel obtained from 10-deacetyl-baccatin III. It shows potent anticancer activity, better than that of taxol, and has better pharmacokinetic properties, such as improved water solubility. It is also a stabiliser of microtubules and is cytotoxic against several human cells. It is used in the treatment of locally advanced metastatic breast cancer and non-small-cell lung cancer [152–156] (Fig. 9).

The preparation of hybrids [157] of natural products (e.g., podophyllotoxin–paclitaxel, camptothecin–podophyllotoxin) is an extraordinary strategy with regard to the preparation of thousands of compounds that might

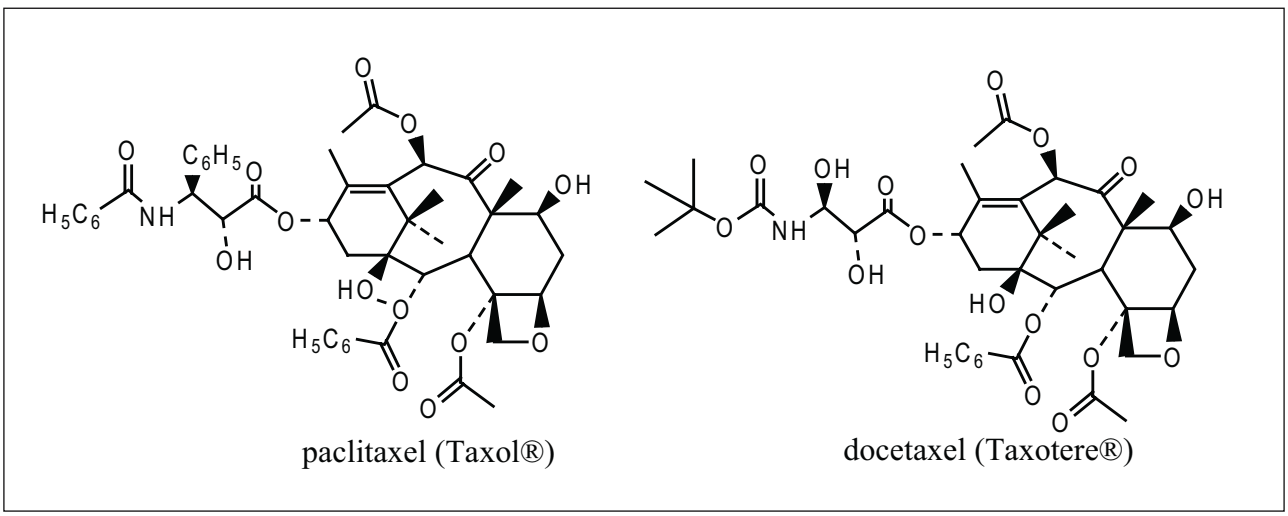

Fig. 9 Paclitaxel and docetaxel

display the pharmacological properties of the two natural compounds that form part of the hybrid, or that might improve the properties of such compounds or their pharmacokinetics.

Other natural anticancer products that have also been subjected to structural modifications in the search for better anticancer drugs are puromycin, mitomycin C, dactinomicin, doxorubicin, daunorubicin, bleomycin, mitramicin, masoprocol and resveratrol, among others [158, 159].

In sum, natural products play an important role in the development of drugs, especially for the treatment of cancer. Podophyllotoxin, camptothecin, vinblastine and paclitaxel are only four examples of lead natural anticancer drugs within the broad arsenal of natural compounds whose structural modification has led to more potent and less toxic compounds than the prototype; the main aim of pharmacomodulation. Additionally, the possibility of generating hybrids of natural products seems to be very promising in the development of new lead compounds with better activity than that of the parent compound.

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