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Adverse drug reactions of anticancer drugs derived from natural sources

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ABSTRACT

Cancer, a life threatening disease adversely affects huge population worldwide. Naturally derived drug discovery has emerged as a potential pathway in search of anticancers. Natural products-based drugs are generally considered safe, compared to their synthetic counterparts. A systematic review on adverse drugs reactions (ADRs) of the anticancer natural products has not been performed till date. We reviewed anticancer drugs, derived from plants, microbes and marine sources with their mechanistic action and reported ADRs. PubMed, ScienceDirect and Scopus were searched through Boolean information retrieval method using keywords “natural products”, “cancer”, “herbal”, “marine drugs” and “adverse drug reaction”. We documented ADRs of natural products based anticancer agents, mechanisms of action and chemical structures. It was observed that majority of the natural products based anticancer drugs possess ample adverse effects, dominantly hematological toxicities, alopecia, neurotoxicity and cardiotoxicity. These findings deviate from the preconceived notion about safer nature of herbal drugs. We also came across some anti-cancer natural products with less/no reported adverse events like Cabazitaxel and Arglabin. Comprehensive pharmacovigilance studies are needed to report ADRs and thereby predicting safety of anti-cancer drugs, either originated from natural sources or chemically synthesized.

1. Introduction

Cancer is one among the life threatening diseases and is pronounced as the cluster of ailments characterized through the uncontrolled progression and metastasis of unusual or anomalous cells. After cardiovascular diseases, cancer is recognized as the second most common reason of death in USA and Europe (Ruiz-Torres et al., 2017). As claimed by world cancer research fund international, top 5 countries with highest cancer rates were Denmark, France (metropolitan), Australia, Belgium, and Norway (https://www.wcrf.org/int/cancer-facts-figures/data-cancer- frequency-country accessed on 20.06.2018). About 60% of the world population and close to half of the global cancer patients live in Asia. Due to diverse factors, the cancer incidences are believed to rise from 6.1 million cases in 2008 to 10.6 million by 2030 (Sankaranarayanan et al., 2014). Similar to USA, cancer is among the leading cause of mortality in India as well and is the cause of 3 million deaths per year (Ali et al., 2011). A recent report entitled ‘Call for Action: Expanding cancer care for women in India (2017)” suggested that cancer prevalence in India is anticipated to increase form 3.9 million in 2015 to 7.1 million by 2020 (https://www.ey.com/Publication/vwLUAssets/EY-Call-for-action-expanding-cancer-care-in-india/$FILE/EY-Call-for-action-expanding-cancer-care-in-india.pdf accessed on 20.06.2018). The women are more prone to occurrence of cancer with 20% higher occurrence rate and 40% higher mortality rate than men (Siegel et al., 2017) and in India, mortality from cervical cancer is higher than rest of the world (Bhaumik, 2013). Globally 8.8 millions of deaths were reported due to cancer, in year 2015 (http://www.who.int/news-room/fact-sheets/detail/cancer accessed on 20.06.2018). Some of the widely used cancer medicines are Bevacizumab, Cyclophosphamide, Cisplatin, Methotrexate, Paclitaxel etc.

Abbreviations: ADA, Adenosine deaminase; ADRs, Adverse drug reactions; Ara-C, Cytarabine; Bax, Bcl-2-associated X protein; Bcl, B-cell lymphoma; DNA, Deoxyribonucleic acid; EMEA, European medicine agency; FADD, Fas-associated death domain protein; ERK, extracellular signal–regulated kinases; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IgE, Immunoglobulin E; IL-6, Interleukin 6; JNK, Jun NH(2)-terminal kinase; MAPK, mitogen-activated protein kinases; MARCKS, myristoylatedalanine-rich C-kinase substrate; MLKL, mixed lineage kinase domain like pseudokinase; PKC, protein kinase C; PUMA, p53 upregulated modulator of apoptosis; RNA, Ribonucleic acid; RIPK, Receptor-interacting serine/threonine-protein kinase; STAT3, Signal transducer and activator of transcription 3; TNF, tumor necrosis factor; TRADD, tumor necrosis factor receptor type 1-associated death domain protein; TRAIL, TNF-related apoptosis-inducing ligand

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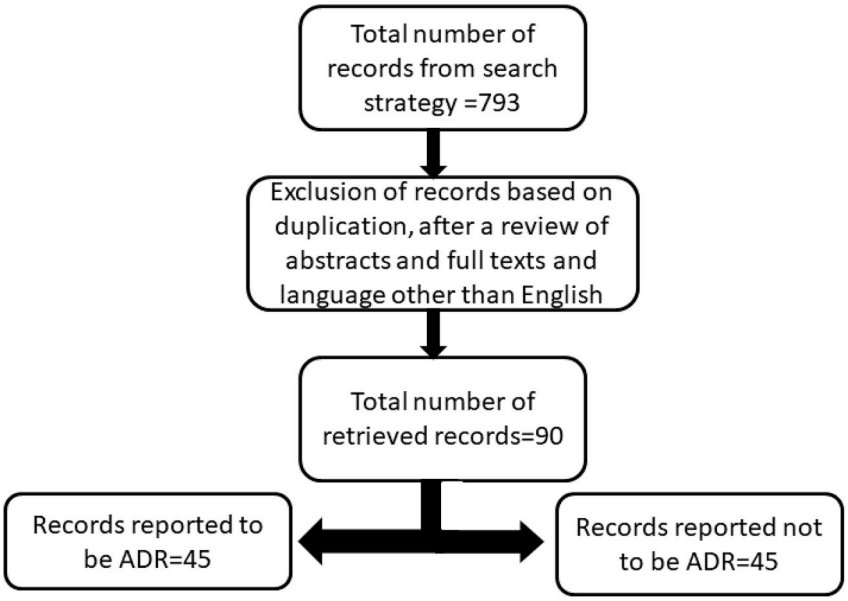


Fig. 1. Flow chart of the search strategy (Some other relevant references were also used to describe the ADRs and their mechanism).

(Huang et al., 2017) which are also associated with numerous serious adverse effects including thromboembolic events, gastrointestinal perforation, pulmonary embolism, cerebral hemorrhage, gastrointestinal hemorrhage, hypersensitivity reactions, anaphylaxis, alopecia (Sitzia and Huggins, 1998; Surendiran et al., 2010; Taugourdeau-Raymond et al., 2012). Since antiquity, plants have been utilized as the integral source of the medicinal preparations for prevention and treatment of various ailments. In the recent past, R&D on natural products have gained tremendous momentum with an interest to include them in the clinical applications, including cancer (Dias et al., 2012; Harvey, 2008; Rawat and Singh, 2018). Newman and Cragg analyzed the US-Food and Drug Administration (US-FDA) approved drugs and concluded that during the year 1981–2010, around 34% of the FDA approved drugs were based upon the small molecules which were derived either directly from the natural resources or their derivatives (Newman and Cragg, 2012). These mainly comprise of tubulin binding anticancer drugs, statins, and immunosuppressants (Butler et al., 2013; Carter, 2011; Cragg and Newman, 2013; Harvey et al., 2015; Mishra and Tiwari, 2011). In another analysis carried out for the year 1940–2014, Newman and Cragg described that anti-cancer natural products or their derivatives included 49% of total 175 FDA approved small molecules (Newman and Cragg, 2016).

Several examples of natural products derived from the plants are available in literature (Atanasov et al., 2015). Most common anticancer products of plant origin are paclitaxel obtained from *Taxus* species, camptothecin from *Camptotheca acuminata* Decne, and vinblastine, vincristine, from *Catharanthus roseus* (L.) G. Don. *Camptotheca acuminata* Decne is a herb which is used in Chinese system of medicine for the treatment of cancer patients (Lin et al., 2014) and *Taxus* has been used in folk medicine against breast and ovarian cancer in Central Himalaya (Wangkheirakpam, 2018). Although, the use of *Taxus* as medicine for cancer in Indian culture was not known during the drug development process and it is claimed to be developed during a random screening method (Atanasov et al., 2015; Cragg and Newman, 2013; Heinrich, 2010; Kinghorn et al., 2011). Various plant derived anticancer molecules which are used clinically are Homoharringtonine from *Cephalotaxus harringtonii* (Knight ex J. Forbes) K.Koch, Ingenolmebutate, isolated from *Euphorbia peplus* sap, Elliptinium, anellipticine derivative isolated from *Bleekeria vitensis* and several others.

Apart from the molecules isolated from natural sources including plants, microbes, etc., various derivatives and analogues have also been developed, approved and used for the treatment of cancer. Besides their isolation directly from natural resources, these have also been synthesized to enable large scale production and use. Synthetic process was mainly adopted because of the supply crisis factor associated with commercial usage of plants and naturally derived products. The overexploitation and unsustainable harvesting lead to population threat to various plants (Atanasov et al., 2015; Cordell, 2011). An estimate suggests that due to unprecedented destruction of medicinal plants, out of 50,000–70,000 medicinal plants species, about 15,000 are threatened with extinction (Brower, 2008). The “taxol supply crisis” is a classic example of this (Cragg et al., 1993). Taxol, effective against ovarian cancer and melanoma is isolated from *Taxus brevifolia* bark and it is present in very small amount. Later, semisynthetic method for taxol synthesis from 10-deacetylbaccatin was developed, which is acquired from the needles of *Taxus baccata* (Cragg et al., 1993; Kingston, 2011; Li and Vederas, 2009; Roberts, 2007).

Despite of burgeoning interest towards the natural medications, researchers have to tackle various challenges during and post drug development process; such as stability, quality and repetitive efficacy, safety and the adverse drug reactions (ADRs). Many studies describe the ADRs of the anticancer drugs (Biswal and Mehta, 2018; Giavina-Bianchi et al., 2017; Henning and Harbison, 2017; Ng et al., 2018; Pugazhendhi et al., 2018; Saini et al., 2015; Visacri et al., 2017), however, a systematic review pertaining to the ADRs from naturally derived anticancer drugs has yet not been done. In this systematic review, we aimed to document the data on ADRs occurred during and/or after the chemotherapy with natural compound based anticancer drugs. The article also describes the mechanisms involved in reported ADRs associated with natural compound based anticancer drugs.

2. Methodology

We collected the scattered information on the ADRs of numerous approved natural product-based anti-cancer drugs. For this purpose, we searched different databases Pubmed, ScienceDirect and Scopus through Boolean information retrieval method using keywords “natural products”, “cancer”, “herbal”, “marine drugs” with “AND” operator followed by “adverse drug reaction” or “ADR” (Pohl et al., 2010). A methodology of the search strategy is presented in Fig. 1.

3. Availability of natural products based anticancer drugs

Combinatorial chemistry-based drug discovery process was the main approach of pharmaceutical industry around 30 years ago, wherein massive number of compounds could be chemically synthesized (Paterson and Anderson, 2005; Ruiz-Torres et al., 2017). However, due to availability of diverse active compounds, natural products based processes of drug discovery have gained potential interest of researchers in recent years. It is an estimate that a minimum 1/3rd of the currently available topmost 20 marketed drugs are originated or derived from natural sources in general and plants in particular (Howitz and Sinclair, 2008; Newman and Cragg, 2007; Ruiz-Torres et al., 2017). It is believed that no other source can be better than nature for identifying the leads for drug discovery, which is evident by the fact that over 60% of the drugs/therapeutics either available in market or in the clinical stage are based on natural products (Brower, 2008). Reliance on use of the natural products for the process of drug discovery is based on presumption that these contain bioactive molecules which are evolved for binding with molecules within the biological system, thereby making these suitable as therapeutics. Furthermore, the unique structures of bioactive molecules may be utilized for the development of analogues with better efficacy (Ruiz-Torres et al., 2017).

Like plants, microbes have also been substantially explored and many antineoplastic agents have been discovered from microorganisms. Microbes derived drugs include cephalosporins from *Cephalosporium acremonium*, penicillins from *Penicillium* species, griseofulvin from *Penicillium griseofulvum* fungus, ivermectins from *Streptomyces* species, lovastatin from *Aspergillus* species, mevastatin from *Penicillium* species and *β*-lactam antibiotics from many fungal taxa (Khazir et al., 2014). Many microorganisms derived secondary metabolites have been discovered in recent years and these antitumor antibiotic agents have emerged as vital chemotherapeutic agents against cancer. Everolimus, a 40-*O*-(2-hydroxyethyl) derivative of sirolimus is one of the anticancer drug of microbial origin, approved by FDA for advanced pancreatic neuroendocrine tumors and angiomyolypoma with tuberous sclerosis complex in 2011 and 2012 respectively (Khazir et al., 2014).

The marine ecosystem is one of the unconstrained source of numerous complex structures and bioactive compounds, and is believed to be a promising source for the drug discovery (Molinski et al., 2009). It is estimated that around half of the total biodiversity present in the globe encompasses the aquatic organisms (Khazir et al., 2014). Spongouridine and Spongothymidine were first two compounds which were isolated from the Caribbean sponge *Tethyacrypta* by Bergman in 1950s which were later considered as the precursor for all nucleoside drugs (Bergmann and Burke, 1955; Bergmann and Feeney, 1951; Suckling, 1991). The molecular scaffolds of compounds originated from the marine natural resources are very specific and make these suitable agents for the drug development. Around 71.02% molecular scaffolds are reported to be utilized solitary by the marine organisms (Kong et al., 2010). Unfortunately, several marine organisms like sponges that contains very potential natural lead compounds are very less populated which leads to scarcity of raw materials for commercialization, thereby the chemical synthesis is only option left for bridging the demand and supply gap (Paterson and Anderson, 2005).

Before 2013, out of total 8 approved marine derived drugs, four were anticancer drugs approved by FDA/European medicine agency (EMEA) and include cytarabine (approved in 1969 for non-Hodgkin lymphoma and acute myeloid leukemia) (Wang et al., 1996), Eribulinmesylate (approved in 2010 for metastatic breast cancer) (Huyck et al., 2011), Brentuximabvedotin (approved in 2011 for anapalstic large cell lymphoma and Hodgkin lymphoma) (Khazir et al., 2014), and Ecteinascidin (approved in 2007 for advanced soft tissue sarcoma) (Abraham et al., 2012; Khazir et al., 2014; Mayer et al., 2010). In 2011, global market of marine derived drugs costed approximately $4.8 billion (Khazir et al., 2014). These natural products based on marine biodiversity have been reported to have unique and diverse mechanisms of action. For instance, Apratoxin A, isolated from cynobacterium *Lyngbya majuscule* acts through reversible inhibition of secretory pathway in several cancer-associated receptors via intrusion with co-translational translocation (Luesch et al., 2006).

4. Adverse drug reactions from natural products based anticancer drugs

Majority of the drugs clinically used as anticancer agents are known to produce various toxic effects (Cragg and Newman, 2005; Saini et al., 2015). The prime focus of cancer chemotherapy is to use selective and suitable drug with an ability to eradicate the malignant cells, without killing the ordinary cells. It is widely accepted fact that the side effects of the anti-cancer therapies are key cause of patients' mortality. ADRs are believed to be as fourth to sixth foremost cause of mortality in hospitalized patients, with around 7% incidence rate (Lazarou et al., 1998; Singh et al., 2017). Anticancer drugs are toxic in nature and usually prescribed to over 50% patients of cancer having low therapeutic index, although their cure percentage contribution is quite less. Moreover, ADRs from the chemotherapeutic agents are now well accepted by the patients as well as health care providers and these are believed to be as an inevitable component of the chemotherapy (Singh et al., 2017).

The patients survival rate for cancer is around 67% and the numbers of cancer surviving patients is estimated to increase by 19 million by 2024 (Abe and Yeh, 2016; Henning and Harbison, 2017). Cardiovascular problems are some of the major adverse events of cancer chemotherapy. Additionally, risk of cardiovascular disease is eight times higher in the cancer survivors than others. It is an estimate that around 50% of survivors of childhood cancer can develop cardiac or vascular damage in consecutive 5–10 years after receiving the cancer chemotherapy (Akam-Venkata et al., 2016; Hamo and Bloom, 2015; Wickramasinghe et al., 2016). Treatment with drugs of anthracyclin category like doxorubicin, idarubicin, mitoxantrone, daunorubicin, idarubicin and other drugs like ifosfamide, cyclophosphamide, and clofarabine results into high cardiac risk. Other drugs such as sorafenib, pertuzumab, trastuzumab are of intermediate risk with low cardiac risk from lapatinib, dasatinib, bevacizumab and imatinib. The detailed review on cardiotoxicity and cardiovascular complication was published elsewhere (Henning and Harbison, 2017). Apart from cardiovascular risk, the chemotherapy has also been found to be associated with enhanced occurrence of cutaneous adverse reactions. Several cutaneous adverse events have also been reported for the well tolerated conventional chemotherapeutic drugs and immunotherapies. These reactions may range from alopecia, acneiform eruption, paronychia to life threatening situations for instance Stevens-Johnson syndrome, toxic epidermal necrolysis, and immune system mediated type B adverse drug reactions (Ng et al., 2018; Roujeau, 2006). Cancer therapeutic strategies like ionizing radiation and various chemotherapeutic agents can also possess the risk of exacerbating and/or inducing different pulmonary injury injuries like lung fibrosis and pneumonitis (Li et al., 2018).

Plant based medicines to combat the adverse reactions associated with drugs has been described in Ayurveda, an ancient traditional Indian medicine system. Several herbs are described which can alleviate the common adverse effects produced by the modern chemotherapeutic agents. For instance, *Bacopa monnieri* with anti-stress and mental strengthening effects, can be beneficial in the management of stress induced insomnia (Chowdhuri et al., 2002; Garodia et al., 2007). Some other plant species like *Ocimum* has anti-depressant properties and therefore could be beneficial to reduce depression commonly seen in cancer patients (Tewari et al., 2015). Association of numerous other herbs with various oncogenes, tumor suppression genes and other targets have been explained previously by Garodia et al. (Garodia et al., 2007).

Details of the ADRs associated with anti-cancer natural products of

Table 1
A detailed description of the adverse drug reactions and mechanisms of approved natural product based anticancer drugs.

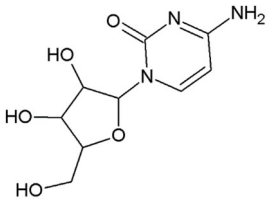
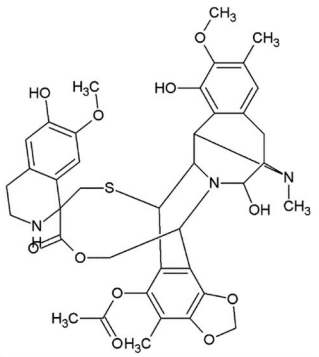
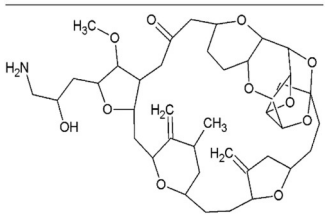
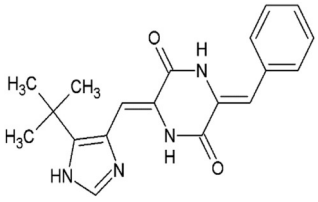
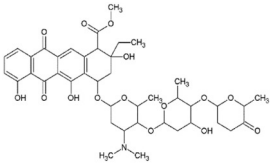
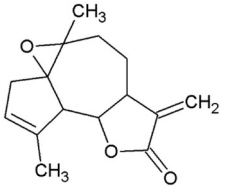
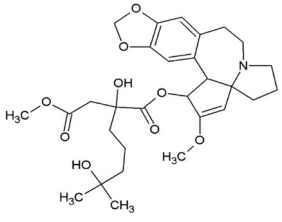
Compound	Structure	Source	Anti-cancer Mechanisms	Adverse drug reaction
Marine products				
Cytarabine (Ara-C)		Sponge Porifera	DNA polymerase inhibition (Mayer et al., 2010; Ruiz-Torres et al., 2017)	Oral mucositis, myelotoxicity, diarrhea and gastrointestinal toxicity, intestinal ulceration, septicemia (Stentoft, 1990)
Trabectedin (E7389)/ Ecteinascidin		Tunicate *Ecteinascidia turbinata*	DNA-sequence specific binding, cancer cell growth inhibition, effect on microenvironment of tumor (Cassier et al., 2008; D'Incalci et al., 2014; Ruiz-Torres et al., 2017)	Liver enzymes elevation (Cassier et al., 2008)
Eribulin		Halichondrin B analogue which is derived from Halichondria okadai a marine sponge	Inhibition of microtubule dynamics growth phase and sequestration of tubulin into non-productive aggregates, microtubule polymerization inhibition, irreversible mitotic block at G2-M phases and apoptosis (Jordan et al., 2005; Smith et al., 2010; Towle et al., 2011)	Neutropenia and asthenia/ fatigue, peripheral neurotoxicity, astrointestinal toxicity, alopecia and mucositis (Gamucci et al., 2014; Jain and Vahdat, 2011)
Plinabulin		Marine fungus *Aspergillus ustus*	Direct action on tumor cells leads to apoptosis (Singh et al., 2011)	Nausea, vomiting, fatigure, tumor pain, fever (Mita et al., 2010)
Plant and microbes derived products				
Aclarubicin		Bacterium *Streptomyces galilaeus*	Inhibition of DNA topoisomerase in the nucleus and mitochondrial dysfunction (Iihoshi et al., 2017)	Hematological toxicities (Adachi et al., 1983) and alopecia (Sezaki et al., 1984)
Arglabin		*Artemisia glabella* Kar. & Kir.	Inhibition of farnesyl protein transferase which is an enzyme responsible for malignant tumor formation (Adekenov, 2016; Shaikenov et al., 2001)	No side effects (Lone and Bhat, 2015)
Homoharringtonine		*Cephalotaxus hainanensis* H.L.Li and Cephalotaxus harringtonia	Protein translation inhibition through prevention of the protein synthesis (early elongation step) by ribosomal A-site interaction (Fresno et al., 1977; Huang, 1975; Lü and Wang, 2014), enhancement of TNF-related apoptosis-inducing ligand (TRAIL)-mediated necroptosis via same signaling pathways	Dyspnoea, hypoxemia, renal toxicity, neutropenia, thrombocytopenia (Daver et al., 2013), animal study showed no apparent side effects (Cao et al., 2015)

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Table 1 (*continued*)

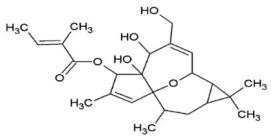
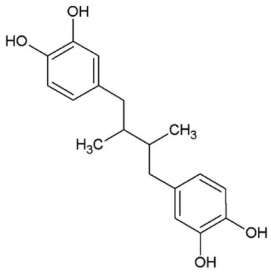
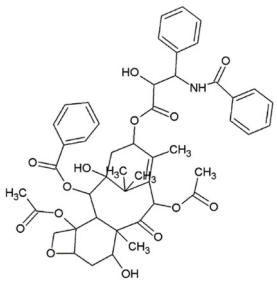
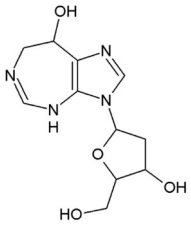
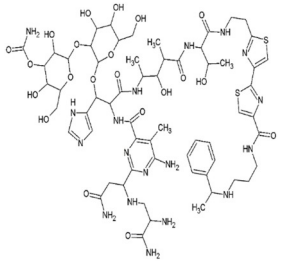
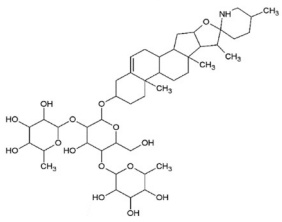
Compound	Structure	Source	Anti-cancer Mechanisms	Adverse drug reaction
			which involves RIPK1/RIPK3/MLKL (Philipp et al., 2015),reversible inhibition of IL-6-induced STAT3 tyrosine phosphorylation and decrease anti-apoptotic proteins expression (Cao et al., 2015)	
Ingenolmebutate		*Euphorbia peplus* L.	A dual mechanism of action and acts as an agonist for the intracellular protein kinase C (PKC) (Rosen et al., 2012; Samrao and Cockerell, 2013) andantibody-dependent cellular cytotoxicity which is neutrophil-mediated (Alchin, 2014)	Moderate or severe skin reactions and produce local short-duration side effects which are well tolerated (Conde-Taboada et al., 2017; Lebwohl et al., 2013)
Masoprocol/ Nordihydroguaiaretic acid		*Larrea divaricata* Cav.	Inhibition of lipooxygenase and cyclin D1 expression in cancer cells, disrupt the filamentous actin cytoskeleton in various cancer cells which is escorted by Jun-NH(2)-terminal kinase and p38(MAPK) activation (Seufferlein et al., 2002)	Hepatotoxicity and nephrotoxicity (Lambert et al., 2002; Rahman et al., 2011)
Paclitaxel		*Taxus brevifolia* Nutt.	Increase the tubulin polymerization to stablize microtubules and microtubules interaction which stabilize against depolymerization and readily depolymerize normal microtubules (Horwitz, 1994)	Alopecia, bradycardia and hypotension, neurotoxicity, peripheral neurological symptoms, hypersensitivity reactions, hepatotoxicity, and mucositis (Walker, 1993)
Pentostatin		Bacterium *Streptomyces antibioticus*	Adenosine deaminase (ADA) inhibitor and accumulation of adenosine and deoxyadenosine in the plasma (Johnston, 2011)	Abdominal pain, appendicitis, pancreatitis, adrenal insufficiency, infections (grade 3 to 4), renal insufficiency, nausea and ulcers (Jacobsohn et al., 2007)
Peplomycin		*Streptomyces verticillus* (mixture of various basic glycopeptide)	Cytocidal action in G2-M phase of the cells (Fujii et al., 1986; Kumazawa et al., 1996)	Anorexia, alopecia, nausea, vomiting and local pigmentation, (Araki et al., 1986)
Solamargines		*Solanum sodomaeum* Drege in DC./*Solanum incanum* L.	Up-regulation of TNF receptors expression (TNF-R1 and TNF-R2) and down streaming of Fas-associated death domain protein (FADD) and TNF receptor type 1-associated death domain protein (TRADD) signaling cascades, activation of mitochondrial pathway of apoptosis (Al Sinani et al., 2016) and downregulate HER2/neu gene expression (Shiu et al., 2008)	Membrane effects in frog embryo (Blankemeyer et al., 1998)

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Table 1 (*continued*)

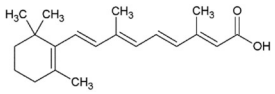
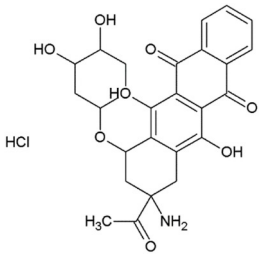
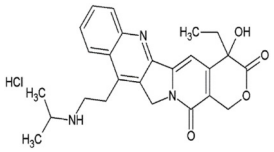
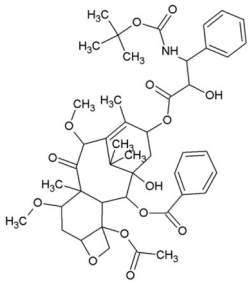
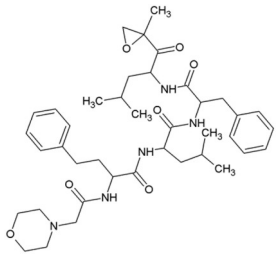
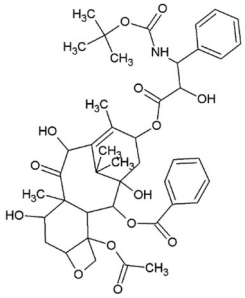
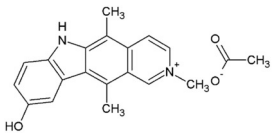
Compound	Structure	Source	Anti-cancer Mechanisms	Adverse drug reaction
Alitretinoin		Naturally-occurring retinoic acid	Modulation of adaptive and innate immune responses via chemokine-induced leukocyte recruitment suppression and inhibitory effect on dendritic cell-mediated activation of T cell (Kislat et al., 2011)	Rashes (Bodsworth et al., 2001), dryness of mouth, lips and skin, flushing, anemia, and erythema, enhance levels of serum cholesterol and triglycerides reduce serum thyroid-stimulating hormone (TSH) levels (King et al., 2014)
Amrubicin hydrochloride		Synthetic molecule which is based upon doxorubicin, derived from *Streptomyces peucetius*	Purified human DNA topoisomerase II inhibitor (Hanada et al., 1998)	Myelosuppression, hematological toxicities and neutropenia (Imai et al., 2017)
Belotecan hydrochloride		Semisynthetic analogue of camptothecin which is isolated from *Camptotheca acuminata* Decne.	Potent inhibitor of topoisomerase I (Kim et al., 2010)	Dizziness, headache, hematological toxicities, neutropenia and lung infection (Park et al., 2016)
Cabazitaxel		Semi-synthetic derivative of 10-deacetylbaccatin III a natural taxoid which is derived from *Taxus* genus	Microtubule dynamics suppression (Azarenko et al., 2014)	
Carfilzomib		Epoxomicin derivative which is obtained from Q996-17 strain (Thermomonospora or related genera of actinomycete) isolated from a soil sample collected from Andhra Pradesh, India	Irreversible and selective inhibition of 20S proteasome (Khazir et al., 2014)	Anemia, dyspnea, diarrhea, fatigue, nausea, thrombocytopenia, lymphopenia, pneumonia, congestive heart failure and acute renal failure (Harvey, 2014)
Docetaxel		Semisynthetic and side-chain analogue of paclitaxel	Microtubular depolymerization inhibitor and attenuate the effect of bcl-xL and bcl-2 gene expression (Pienta, 2001)	Anaphylactoid reactions, shock (Heike et al., 2005), edema, scleroderma-like skin changes (Battafarano et al., 1995)
Elliptiniumacetate		Acetate salt of elliptinium which is ellipticine derivative isolated from *Bleekeria vitiensis* (Markgr.) A.C.Sm.	Inhibition of topoisomerase II and an intercalating agent, elliptiniumis responsible for the stabilization of topoisomerase II cleavable complex and induce DNA ruptures, thus inhibits DNA replication, protein and synthesis of RNA (Rouëssé et al., 1993)	Diarrhea, nausea, vomiting, xerostomia, (Buzdar et al., 1990) andimmune-mediated haemolytic reactions (Rouëssé et al., 1993)
Epirubicin HCl		Hydrochloride salt of the 4′-epi-isomer of doxorubicin which is obtained *Streptomyces peucetius*	DNA and RNA synthesis inhibitor (Tsukagoshi, 1990)	Cardiotoxicity but lower than doxorubicin (Tsukagoshi, 1990)

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Table 1 (*continued*)

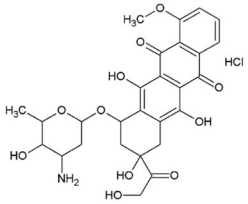
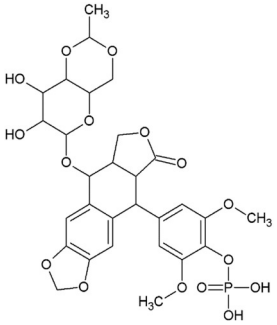
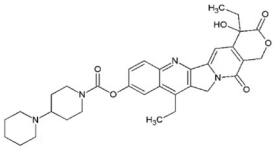
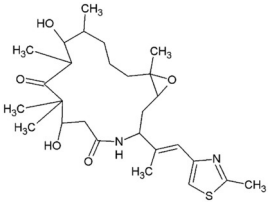
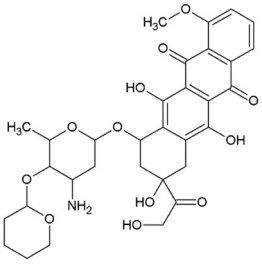
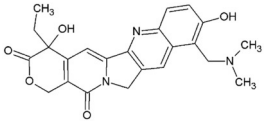
Compound	Structure	Source	Anti-cancer Mechanisms	Adverse drug reaction
				
Etoposide phosphate		Phosphate salt of semisynthetic derivative of podophyllotoxin which is obtained from *Podophyllum* plant.	DNA synthesis inhibitor and breakdown the DNA strand, stabilize topoisomerase II cleavable complex and has major effect at late S-G2 interface cell cycle (Henwood and Brogden, 1990; O'Dwyer et al., 1985)	Bronchospasm, chest discomfort, dyspnoea, hypersensitivity reactions and hypotension (Siderov et al., 2002)
Irinotecan		Semisynthetic derivative of camptothecin which is extracted from *Camptotheca acuminata* Decne.	Topoisomerase I inhibitor (Goldberg et al., 2004; Hsiang et al., 1985).	Rash (Peréz-Soler and Saltz, 2005), diarrhea, nausea, vomiting, febrile neutropenia (Goldberg et al., 2004)
Ixabepilone		Semisynthetic analogue of epothilone B isolated from *Sorangium cellulosum* a myxobacterium	Stabilize microtubules and induce apoptosis and a highly active microtubule inhibitor, induce G2-M cell cycle arrest (Bode et al., 2002; Lee et al., 2001; Schiff et al., 2009) enhance caspase-2 activity (Rojas-Espaillat et al., 2005), induction of p53 upregulated modulator of apoptosis (PUMA) expression leads to p53-mediated activation of death effector Bax (Vahdat, 2008; Yamaguchi et al., 2004)	Peripheral neuropathy and neutropenia (Schiff et al., 2009)
Pirarubicin		Analogue of doxorubicin	Cell cycle arrest at G0/G1 phase, suppression of PCNA, Bcl-2, cyclin E, cyclin D1, expression, and amplified Bax expression (Liu et al., 2010)	Leucopenia and mucositis (Iguchi et al., 2004)
Topotecan		Semisynthetic derivative of camptothecin which is isolated from *Camptotheca acuminata*	Topoisomerase I inhibitor (Kollmannsberger et al., 1999) interrupt DNA replication in affected cells leads to cell death (Arun and Frenkel, 2001)	Alopecia (Kollmannsberger et al., 1999), hematologictoxicity, thrombocytopenia and neutropenia (Anastasia, 2001)
Valrubicin		Semisynthetic derivative of doxorubicin	Reduce cell proliferation, encourage apoptosis, stimulation of PKCα activity and downstream signaling was also explored through measurement of phosphorylated	Reversible local bladder symptoms(Steinberg et al., 2000)

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Table 1 (*continued*)

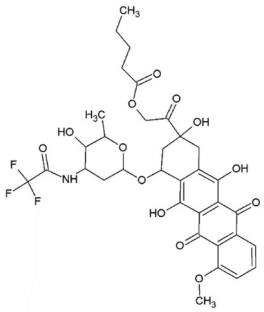
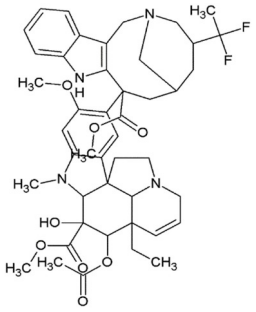
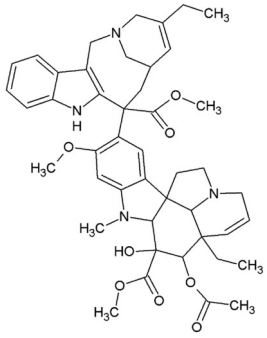
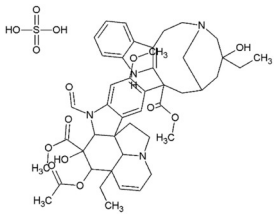
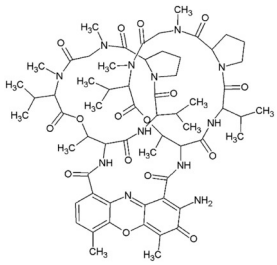
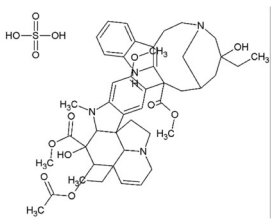
Compound	Structure	Source	Anti-cancer Mechanisms	Adverse drug reaction
			myristoylatedalanine-rich C-kinase substrate (MARCKS) and extracellular signal-regulated kinases (ERK) 1/2 amount of valrubicin-stimulated keratinocytes (Laugesen et al., 2013)	
Vinflunine		Bi-fluorinated derivative of vinorelbine, a semi-synthetic vinca alkaloid	Microtubule inhibitory effect (Jordan et al., 2008)	Bone marrow suppression/ myelosuppression, dose limiting toxicity, constipation, febrile neutropenia (Gerullis et al., 2017; Souquet et al., 2010; Tournoux-Facon et al., 2011)
Vinorelbine		Vinorelbine is a semisynthetic *Vinca* alkaloid.	Inhibition of tubulin dimers polymerization into microtubules, which in line disrupts formation of mitotic spindle and preclude cell division. Thus promotes cancer cells apoptosis (Faller and Pandit, 2011)	In combination with neutropenia, thrombocytopenia, and vomiting, leukocytopenia (7%), and anemia (Faller and Pandit, 2011)
Vincristine sulfate		Sulfate salt of vincristine isolated from *Catharanthus roseus*	Inhibition of microtubule formation after binding of vincristein to tubulin. The metaphase arrest leads to mitotic spindle disruption. Also can act via interference with protein and nucleic acid through blocking of utilization of glutamic acid and specific for the M and S phases (Lee et al., 2013)	Optic neuropathy(Weisfeld-Adams et al., 2007) similar to vincristine (Yan et al., 2012)
Dactinomycin		Actinomycin a species of Actiitonzyces isolated from the soil	Selective inhibition of rRNA, action on specific DNA site with high binding affinities (Lindell, 1976)	Neutropenia and emesis (Moore et al., 1999)
Vinblastine sulfate		Vinblastine Sulfate is the sulfate salt of vinblastine, isolated from *Catharanthus roseus*	Microtubule inhibition (Zu et al., 2009)	Nausea, diarrhea, vomiting, paresthesias, leukopenia, skin rash, and aggravation of a peptic ulcer (MacDonald and Lacher, 1966)
Doxorubicin hydrochloride		Hydrochloride of doxorubicin		

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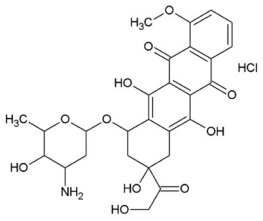
Table 1 (*continued*)

Compound	Structure	Source	Anti-cancer Mechanisms	Adverse drug reaction
			Topoisomerase II inhibition (Ravid et al., 1999)	Cardiotoxicity, nausea, vomiting, gastrointestinal problems, alopecia, and neurological disturbance(Oktay and Pornsak, 2012)

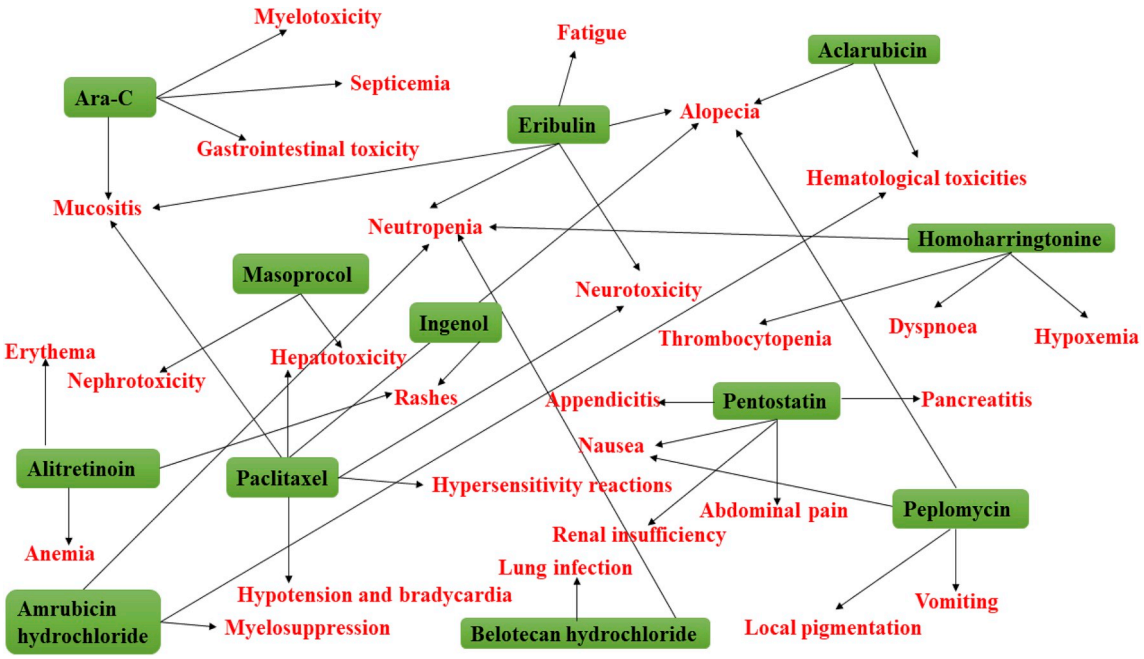


Fig. 2. Some widely used natural products based anticancer drugs and their adverse drug reactions (References consulted: Stentoft, 1990; Gamucci et al., 2014; Jain and Vahdat, 2011; Adachi et al., 1983; Sezaki et al., 1984; Cao et al., 2015; Daver et al., 2013; Conde-Taboada et al., 2017; Lebwohl et al., 2013; Jacobsohn et al., 2007; Bodsworth et al., 2001; King et al., 2014; Walker, 1993; Araki et al., 1986; Imai et al., 2017; Imai et al., 2017; Park et al., 2016).

plants, microbial and marine origin, along with the mechanisms of action, chemical structures and sources are summarized in Table 1.

5. Anticancer natural products related ADRs and their possible mechanisms of action

According to a very easy definition, an ADR is an unwanted or undesirable response to a drug. Such response may or may not be anticipated and most of the times such response is independent of the therapeutic effect of the drug (Anderson, 1992). A metanalysis of prospective studies revealed an extremely high incidence of 6.7% reported for serious ADRs and 0.32% was of fatal ADRs on hospitalized patients (Lazarou et al., 1998).

Usually ADRs are referred as allergies by both physicians and patients but “allergy” may be inaccurate and imprecise word for ADRs, as in several ADRs cases the mechanisms are not associated with the immune system (Rieder, 1994, 1993). Classen et al. conducted a study on 36,653 patients admitted in a hospital over one year duration and found that approximately 2% patients admissions were either for diagnosis or for therapy of ADRs and it was also reported that around 0.2% of these reports were life threatening and severe (Classen et al., 2005). ADRs also have significant economic impact and pose an estimated economic burden of about US$3 billion per year in therapy, diagnosis and screening (Rieder, 1994, 1993).

Generally natural products or their derivatives are considered safe, however, it was found that natural products based anticancer drugs also cause many side effects. Some of the prominent adverse effects are oral mucositis, myosupression/myotoxicity, abdominal pain, hepatotoxicity, diarrhea, elevation of liver enzymes, septicemia, hematological toxicities including neutropenia, asthenia, fatigue, alopecia, skin reactions and rashes, cardiovascular toxicity including bradycardia, hypotension and congestive heart failure, hypersensitivity reactions, adrenal insufficiency and renal failure, infections, nausea, vomiting, ulcer, anorexia, dryness of mouth, dyspepsia, anaemia, thrombocytopenia, pneumonia, anaphylactic shock and xerostomia. Among these, neutropenia, alopecia, hematological toxicity, hepatotoxicity and cardiotoxicity were the most common ADRs reported from different drugs. Mechanisms of few of the ADRs have been described. A schematic representation in Fig. 2 shows the relationships of different natural product-based drugs with the ADRs.

Neutropenia is considered as a life threatening and serious adverse event and happens in response to intake of varieties of drugs, including anticancer ones. It is an idiosyncratic reaction which is either immune mediated or may occur due to damage in the myeloid cells. The natural product-based drugs may sometimes cause considerable decline in the neutrophil count. Although, the exact mechanism for the neutropenia associated with intake of natural anticancer drugs is not extensively studied however, the mechanism of neutropenia associated with other

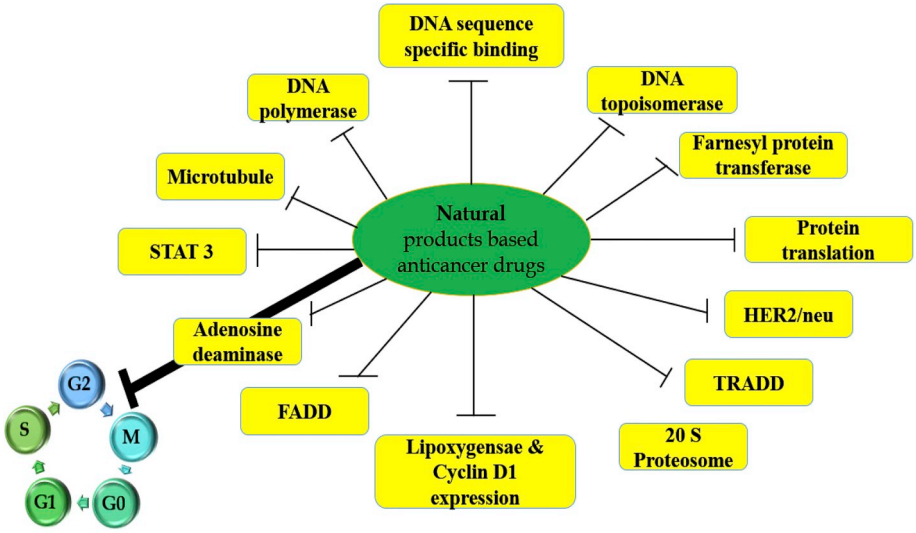


Fig. 3. Representation of the prime mechanisms of action of various natural products based anticancer drugs used clinically.

anticancer drugs has been well investigated. One of the mechanism involves production of antibodies against neutrophils, as observed in case of rituximab, a well-known drug used for various types of cancers (Moore, 2016; Smith et al., 2006). Another possible mechanism may be the disturbance of granulocytes homeostasis through chemokine stromal-derived factor-1, which interacts with the recovery of B-lymphocytes. Neutropenia may also happen due to the immunoglobulin G (IgG) Fc receptor (FcγR) polymorphism. Patients having FcγR polymorphism have been reported to depict more neutropenia incidents (Weng et al., 2010).

Although, drug induced alopecia is one of the main adverse effect of most of the anticancer drugs, however, not much information is available regarding its mechanism, except few case reports (Turkoglu, 2013). Alopecia is emotionally as well as psychologically distressing for the patients (Hussein, 1993) and both of its stages (anagen, telogen effluvium) have been found to be associated as adverse reactions to different drugs (Turkoglu, 2013). Botchkarev, in a review discussed in detail about the molecular mechanisms of chemotherapeutic agents induced alopecia in various animal models (Botchkarev, 2003), wherein, possible role of p53 mediated and p53 independent mechanisms were suggested. Additionally, the authors also advocated the development of human models to explore the molecular mechanisms of apoptosis induced in the hair follicles by various chemotherapeutics (Botchkarev, 2003).

Hypersensitivity reactions are another major ADRs reported from the natural products based anticancer drugs and explained as an immunological response to drug (Zanotti and Markman, 2001). Molecular mechanisms of various hypersensitivity reactions due to different anticancer drugs are still not properly understood. The hypersensitivity reactions are quite unpredictable and may be fatal sometimes. In most of the cases, such reactions are related to taxanes (Boulanger et al., 2014). Hypersensitivity caused by paclitaxel is supposed to be non-fatal (Weiss et al., 1990), however, fatal cases are also reported in the available literature (Kloover et al., 2004). Different mechanisms have been postulated for the general hypersensitivity reactions and encompasses IgE mediated degranulation of mast-cells (Dye and Watkins, 1980; Weiss et al., 1990; Weiss and Baker, 1987), non-IgE mediated idiosyncratic mast cell deregulation (Gelderblom et al., 2001) and sometimes complement activation too (Szebeni et al., 2001). In the fatal cases of paclitaxel hypersensitivity, the casualty has been suggested to be not due to IgE mediated hypersensitivity but by one of the other two mechanisms (Kloover et al., 2004).

Recently a meta-analysis covering from the data of 93 clinical studies and 18,208 patients suggested the use of different antioxidants may ameliorate the chemotherapeutic induced toxicity and also recommend that use of antioxidants while chemotherapy can not only increase the therapeutic efficacy but also the patient survival time (Singh et al., 2018).

6. Mechanistic insight on the anticancer actions

It was observed that natural products due to their diverse and complex structures are able to target the cancer cells by several distinct mechanisms. Fig. 3 shows different mechanisms by which the natural product based anticancer drugs are predicted to act. The anticancer natural compounds exert their effects through wide range of mechanisms prominently by inhibition of various DNA enzymes and signaling pathways. The details on the mechanisms of anticancer action of naturally derived drugs are presented in Table 1.

7. Conclusion

Emerging interest and potential outcomes from natural products had led to substantial increase in drug discovery in terms of new chemical entities as well as the active pharmaceutical compounds for cancer chemotherapy. It is well reported that many naturally derived drugs exert the adverse drug reactions along with their therapeutic effects. Clinical trials focusing on the adverse drugs events of the natural products-based drugs are required to augment the safety and quality of life of patients. Achieving accuracy in assessment of adverse events and symptoms by clinician is a major challenge. Several reports highlight the non-sensitivity and non-specificity of the physician in ascertaining cancer therapy associated adverse events. It is also evident from few reports wherein lack of consistency was observed between the trial database and published findings. These may be surpassed through designing better tools for collection and analysis of ADR data. Additionally, large scale pharmacovigilance studies are required at global front to record the adverse drug events associated with cancer therapy. The precise understanding of safety issues associated with anticancer natural products will facilitate faster approval of safer drugs in future.

Author contributions

DT; data sourcing, analysis, preparation of the draft, PR; technical review of data and inputs and major editing, PKS: conceptualization, editing, critical revision and supervision, all authors have substantially contributed.

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Conflicts of interest

The authors declare no conflict of interest.

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