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Anticancer potential of natural products: a review focusing on Sri Lankan plants

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1. ABSTRACT

In the pharmaceutical industry, the expected surge in production of new therapeutic entities promised by technological advances, such as high-throughput screening, synthetic libraries and advances in molecular biology and genomics, has not materialized. The unique structural diversity of natural products continues to provide opportunities to discover novel compounds. Secondary metabolites, active components of natural products such as marine organisms, microbial organisms and terrestrial plants, are particularly exciting untapped resources for exploration as medicines. Sri Lanka is home to around 3700 plant species, half of which are considered as medicinal plants. Seventy per cent of the Sri Lankan population relies on this plant-based traditional medicine system for treating various illnesses such as tumors. As such these medicinal plant sources should be used to conquer terminal diseases and for prevention of diseases. Sri Lankan researchers have found several plant species that possess cytotoxic activity. This review summarizes the current information regarding the Sri Lankan plant materials that possess anticancer properties.

2. THE STATUS OF NATURAL PRODUCTS IN DRUG DISCOVERY

Natural products have been a source for the successful development of drugs (1). For many years, natural products have played a major role in human health. Despite this long period of historical use, it was only in the 19th century that compounds from natural products such as plants were isolated and characterized. The first commercially available pure natural product was morphine (Figure 1), which was marketed by Merck in 1826 (2). Pharmacist Friedrich Sertürner isolated morphine from *Papaver somniferum* (opium poppy). This initiated an era wherein drugs from plants could be isolated, studied and administered in precise doses (3-4). The production of aspirin (Figure 1) by Bayer followed in 1899. This was a semi-synthetic pure drug (5) derived from salicylic acid and was initially isolated from number of willow species (*Salix*) in 1828 (6).

The investigation of natural products in order to discover novel therapies reached its peak in the 20th century, resulting in a pharmaceutical landscape heavily influenced by non-synthetic molecules. Analysis of developed therapies over the past 30 years or so reveals that ~ 40% of new chemical entities are natural products or are inspired by natural products (7-10). Despite this success, however, over the past two decades pharmaceutical companies have deemphasized natural product research. A possible reason is that natural products are deemed to be incompatible with drug discovery approaches based on novel techniques:

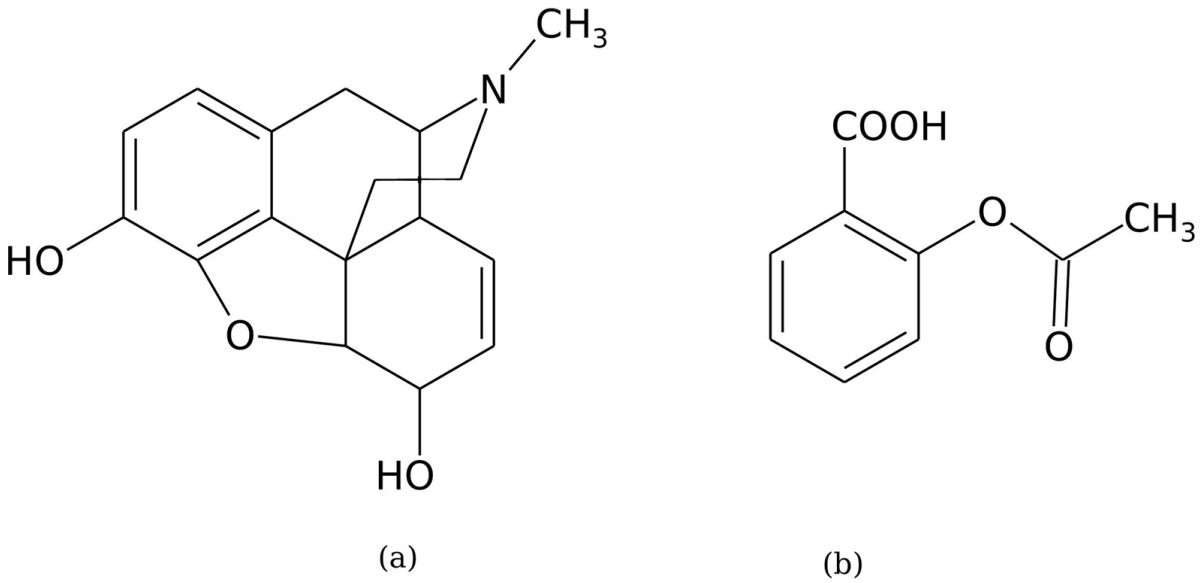


Figure 1. Compound structures of (a) Morphine and (b) Aspirin.

high-throughput screening (HTS); combinatorial chemistry, offering drug-like screening libraries and advances in molecular biology and genomics, which increase the number of molecular targets and strive for shorter drug discovery timelines. In addition, big pharmaceutical companies have reduced their research efforts into infectious disease therapy–a huge area in which natural product discovery was relevant, and there are concerns about repeated isolation of known compounds and uncertainties with regard to collection of biomaterial (7, 11-14). Although novel techniques have overtaken natural product-based drug discovery, the surge in productivity has not increased the number of new chemical entities (1, 15). This demonstrates the importance of natural product research. Experts who continue to develop novel drugs from plants and other natural sources insist that nature is the best guide for discovering new therapies as organisms harbor medically useful substances (16-19).

Metabolism, occurring in all living organisms, is a collection of chemical processes necessary to maintain life. A number of compounds, known as metabolites, result from these processes. These metabolites can be divided into two major categories depending on their origin and function: primary metabolites are directly involved in development and reproduction while secondary metabolites are indirectly involved in metabolism by maintaining homeostasis. Secondary metabolites from natural sources have made a vital contribution to the development of various drugs (20-22), and there are exciting untapped natural sources of secondary metabolites around the globe yet to be explored for medicine development. Examples of these resources include marine organisms, microbial organisms and terrestrial plants (15, 23-24).

2.1. Marine organisms

The, sea is the world's largest unexplored resource. More than 70% of the earth is covered by oceans, representing over 95% of the biosphere. Experts estimate that the biological diversity of oceans is larger than that of tropical rain forests. The concept of medicines from the ocean is relatively new compared to medicines from microorganisms and terrestrial plants (25). In 1951, Werner Bergmann reported the isolation of unusual nucleosides from the sponge *Cryptotethia crypta* collected near the coast of Florida, USA. Out of these compounds chemical derivatives such as ara-A (vidarabine) with significant antiviral properties and ara-C (cytarabine) (Figure 2) with anticancer properties were developed (25-26). Marine organisms are very rich sources of biologically active secondary metabolites. This could be because, when these secondary metabolites are released into the water they are swiftly diluted, which may have a highly potent effect within water. Further, there is a high level of competition among marine organisms due to the high number of species coexisting in a restricted habitat, which is good for sustainability. Absence of light, extreme pH levels and water current are additional growth-limiting factors that fuel this competition. As a result of such competition many of the species have evolved to have chemical adaptations, and have developed secondary metabolites that may be used to

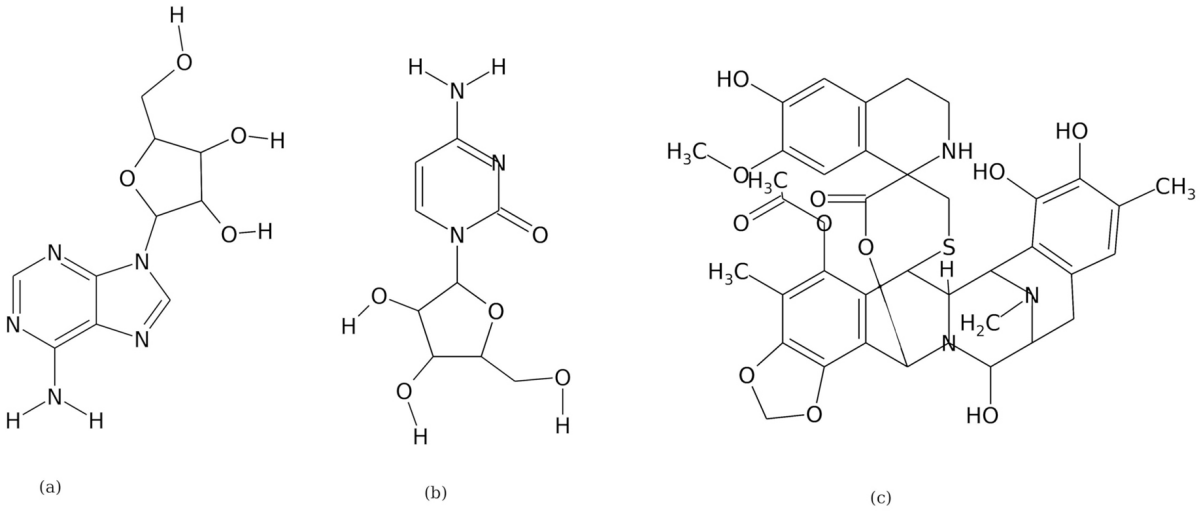


Figure 2. Compound structures derived from marine organisms (a) ara-A (vidarabine) (b) ara-c (cytarabine) and (c) Trabectedin.

defend against predation, or overgrowth by competing species, or conversely, to subdue motile prey species for ingestion (27-29). Secondary metabolites of marine species have shown a vast array of properties including antitumor, antiviral, antibacterial, antimalarial, antifungal, antiinflammatory, and antilipidemic activities (30-32). This illustrates that the marine environment is home to a rich source of bioactive compounds. In a National Cancer Institute (USA) preclinical cytotoxicity screen, ~ 1% of the tested marine samples showed antitumor potential versus 0.1% of the tested terrestrial samples (33). For instance, as part of the screen, the marine tunicate *Ecteinascidia turbinate* was found to have anticancer activity and Trabectedin (Figure 2), a marine alkaloid, was isolated (33). This agent gained approval by the EU for the treatment of soft-tissue sarcoma and relapsed ovarian cancer. It is also undergoing clinical trials for the treatment of breast, prostate and pediatric sarcomas (34-36). There remains an enormous number of marine species yet to be explored in the quest to find novel drugs and drug leads (37).

2.2. Microbial organisms

Bacteria and fungi as living organisms have the ability to produce secondary metabolites or small-molecule natural products (38-41). The discovery of the antibacterial agent penicillin (Figure 3), isolated from the filamentous fungus *Penicillium notatum* by Alexander Fleming in 1929, ushered a new era in medicine. This discovery led to the investigation of number of novel bioactive agents (15, 42). In 1943, Selman Waksman explored microbial sources for novel natural products which led to the isolation of streptomycin (Figure 3) which was the first therapy for tuberculosis, from *Streptomyces griseus*. Despite the success of these agents, currently however, there is an increase in the frequency of multidrug resistance and pan resistant strains which is a huge concern in the fight against pathogenic bacteria. Many of the antibiotics which are used in the clinic today were discovered before the 1970s and recent reports have shown the danger of antibiotic resistance with over two million infections and over 23,000 deaths annually in the USA alone. This demonstrates the need for new antibacterial research using microorganisms (43-44). Nevertheless, due to the structural diversity of microbial sources, many other vital therapies apart from antibacterial agents have been discovered. For example, antineoplastic antibiotics extracted from microorganisms are among the most significant of the cancer chemotherapeutic agents. Members of the anthracycline class of drugs extracted from *Streptomyces* include mitomycin, doxorubicin and daunomycin (Figure 3) (45-47). Further examples of therapeutic agents discovered in microorganisms include immunosuppressive agents such as rapamycin and cholesterol-lowering agents such as mevastatin (Figure 3). Advances of genetics especially the use of ribosomal RNA sequencing as a microbial species profiling tool has begun to uncover a vast diversity of novel microbes from terrestrial and marine environments. This huge collection of microorganisms' has exposed unexploited natural product chemistry that has eventually led to the development of metagenomics, which helps to explore microorganisms who are recalcitrant to culturing. These new approaches will help to detect microbial natural products that have novel bioactive metabolites with distinguishing functionalities. Hence, there is an enormous reservoir of natural compounds which could be developed from microorganisms to treat various diseases including cancer (41-43).

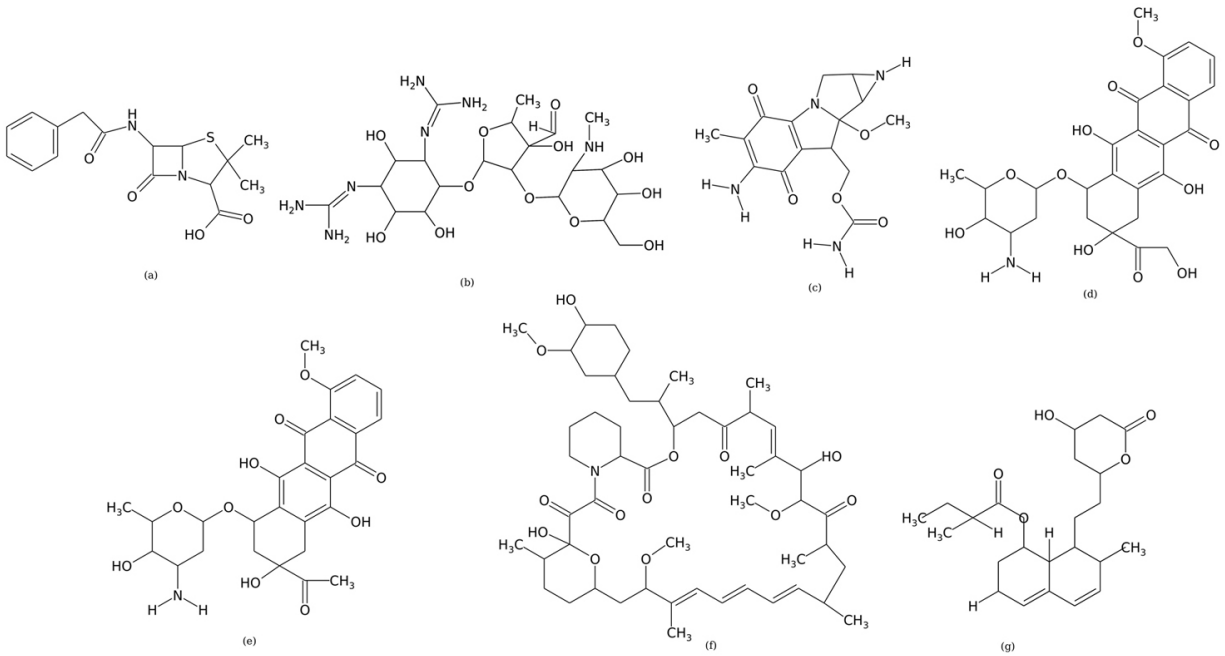


Figure 3. Compound structures derived from microbial organisms (a) penicillin, (b) streptomycin (c) mitomycin, (d) doxorubicin (e) daunomycin (f) rapamycin and (g) mevastatin,

2.3. Terrestrial plants

According to the world health organization (WHO), ~ 65% of the world's population relies on traditional medicines derived from terrestrial plants for their primary healthcare needs (2, 48). Plants have formed the basis of traditional medicine systems used for thousands of years and produce a remarkable diverse array of secondary metabolites. These metabolites have been mainly used to develop antibacterial and anticancer agents and until very recently many blockbuster drugs were derived from only plant sources (49). As well as morphine and aspirin (Figure 1), some of the other examples of medicinal compounds obtained from plant sources include artemisinin (Figure 4), isolated from a Chinese plant *Artemisia annua,* traditionally was used for malaria, and silymarin (Figure 4), extracted from the seeds of *Silybum marianum*, used for the treatment of liver diseases (2). The greatest impact of plant-derived drugs has been in the treatment of cancer. American Indians used extracts from the roots of *Podophyllum peltatum*, (mayapple) for the treatment of skin cancers and venereal warts many years ago (50-51). In the 1950s, the isolation of vinblastine and vincristine (Figure 4) from the leaves of the field-grown *Catharanthus roseus* plant began the modern-day usage of plant-based anticancer agents (52-55). These vinca alkaloids have contributed to long-term remissions in Hodgkin's lymphoma, breast cancer, non-small cell lung cancer, advanced testicular cancer and Kaposi's sarcoma (56). Another promising agent is paclitaxel (Taxol) (Figure 4), obtained from the bark of Pacific yew *Taxus brevifolia* (18). Paclitaxel is used mostly in the treatment of breast cancer and ovarian cancer. Other analogues of paclitaxel, such as docetaxel (Figure 4) were developed: semi-synthetic docetaxel is used in the treatment of metastatic breast cancer (57). Herbal medicines, dietary supplements and edible plants are also used in the prevention of cancer by virtue of their capacity to target cancer initiation, promotion and progression. Plant-based cancer chemopreventive agents, developed in the laboratory and evaluated using clinical studies, include curcumin from turmeric, genistein from soybean, luteolin from green vegetables such as broccoli, cabbage and cauliflower and resveratrol from grapes (Figure 4) (4, 24, 58-62). As such, identifying novel preventive agents from natural products may help to prevent or delay the onset of cancers and may prove useful in combination with existing therapies to minimize recurrence and metastasis in patients with cancer (63-65). Characterization and isolation of bioactive compounds from medicinal plants continue today although the search has diminished to a certain extent. Even if an isolated compound does not find useful as a drug, it may serve as a drug lead for developing novel pharmaceutical drugs. Due to the long history of human use and co-evolution of plants and humans, phytochemicals from plants may provide a safer and more holistic approach to disease treatment and prevention (48).

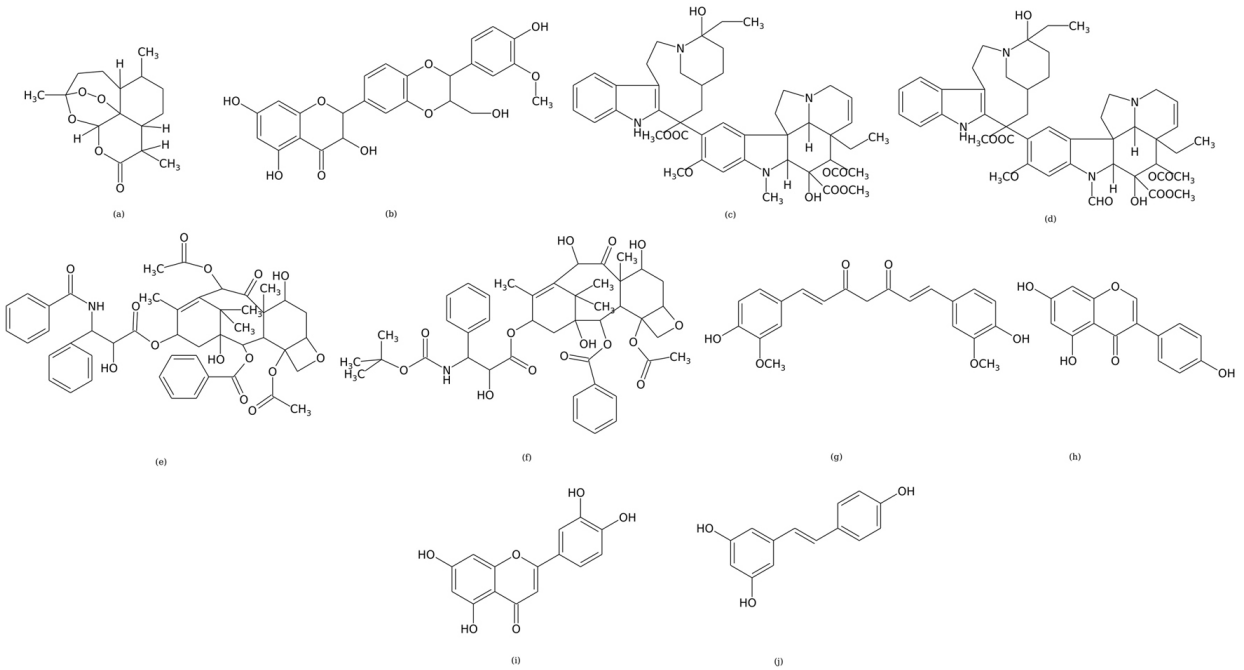


Figure 4. Compound structures derived from terrestrial plants (a) artemisinin (b) silymarin (c) vinblastine (d) vincristine (e) paclitaxel (f) docetaxel (g) curcumin (h) genistein (i) luteolin and (j) resveratrol.

2.4. Traditional medicine system of Sri Lanka

Sri Lanka is home to ~ 3700 floral species, ~ 894 of which are endemic to the country and a little less than half are currently considered as threatened (66-69). The total plant life ranges from that found in equatorial rain forests to that found in dry zones; temperate-zone plants are found in the highlands. (70). In Sri Lanka, ~1430 plant species representing 181 families are considered as medicinal plants. Currently ~ 625 Sri Lankan plant species are used for traditional medicinal purposes and out of these ~ 200 species are commonly used (67). The most commonly used (> 50,000 kg/year) medicinal plants in Sri Lanka include *Centella asiatica, Zingiber officinale, Sesamum indicum*, *Terminalia chebula*, *Terminalia bellirica*, *Phyllanthus emblica*, *Vitex negundo*, *Asparagus racemosus*, *Trachyspermum roxburghianum*, *Azadirachta indica*, *Pavetta indica* and *Indigofera tinctoria*. These species are major ingredients in more than 50 medicinal formulae. According to a 2001 survey conducted by the International Union for Conservation of Nature, the demand for herbal material in the island was 3,864,760 kg with a value of 386 million LKR in the year 2000. Due to the lack of systematic production in Sri Lanka, ~ 1,500,000 kg of herbal material is imported annually, costing ~ 125 million LKR. Local cultivation of the imported plants would therefore save a considerable amount of foreign exchange since most of these plants are said to be well adapted to Sri Lankan climatic conditions. Further, the traditional medicine practice is critically dependent on an uninterrupted availability of plant material. However, adulteration and illegal collection of plant material from forests are matters of concern. Adulteration could be evaluated by methods such as chemical fingerprinting and genomic testing (e.g. DNA barcoding), which are proven useful techniques for identifying plants. Steps should also be taken to create awareness among local farmers about medicinal plants and their economic value so that they could preserve and cultivate valuable plants. Thus, standardized protocols should be implemented for the collection of plant material in the country. Various parts of plants are collected for medicinal purposes in Sri Lanka: leaves (22.2%), roots (17.9%), seeds (12.8%), bark (12.5%), fruits (9.3%), whole plant (8.8%), stem (6.3%), flowers (6.2%) and latex (0.4%) (68). Generally, traditional medical preparations take the form of decoctions, juices, pastes, powders, wines, oils, tablets and capsules. Strict quality control methods should be followed in the preparation of medicines with herbs to ensure safety and efficacy.

In Sri Lanka, the traditional medicine system, using local resources, has been practiced for more than 5000 years in the treatment of various diseases, including those of complicated etiology such as

cancer (71). Building of hospitals was initiated by Sri Lankan kings including Pandukabaya (437-367 B.C.), Dutugamunu (161-137 B.C) and Buddhadasa (341-370 A.D). These hospitals had patient facilities for both monks and laity. Medicinal boats were found in the archaeological remains of hospitals built in the city of Anuradhapura in the 4th century (72). These boats were used to treat various conditions, including arthritis and snake bites, by immersing the patients in a bath filled with herbal oils. Moreover, many more hospitals had been built by kings of Sri Lanka for the ill, crippled and the blind, and the ruins can be found in places such as Mihnitale, Medirigiriya and Dighavapi. Excavations of some of these hospital sites have revealed medicine grinders, ceramic jars for the storage of medicines, mini scales, pairs of scissors, forceps and scalpels, thus providing ample evidence for the practice of medicine and surgery (73). According to ancient history, King Buddhadasa was known as a renowned physician and he documented his healing practices in "Sararthasangrahaya". Further, King Agrabodhi VII (766-772 A.D.) conducted research pertaining to medicinal substances and studied medicinal plants from all over Sri Lanka to determine which plants were beneficial for the sick. Thus, these facts demonstrate that medieval Sri Lanka had a rich history of medicines used for the wellbeing of the people; this information is still used by some local medical practitioners (73-74). At present, the island maintains a rich traditional medicine system which caters for ~ 70% of the population (75). This medicinal system comprises of ayurveda, siddha, unani and deshiya chikitsa (indigenous medical system) (76-77). Both ayurveda and siddha systems were introduced by India to Sri Lanka (78). The ayurveda system comprises single herbs and poly herbal formulations while the siddha system comprises of mineral preparations (79). The unani system was introduced by Arabs who came to Sri Lanka for trading purposes. Some of the medicines from siddha and unani are incorporated within the ayurveda system and these two systems are mostly practiced by the Tamil and the Moor communities of Sri Lanka (80). The deshiya chikitsa system has prevailed in Sri Lanka for many years and the knowledge has been passed from generation to generation; some of the indigenous medicine practitioners are decedents of families with secret formulae to cure illnesses. This Sri Lankan indigenous system is famous for several disciplines, such as fractures, snake poisoning, eye diseases, tumors, burns and mental disorders (81). Nevertheless, the Sri Lankan version of the traditional medicine system and the ayurveda system have been integrated to some extent in practice over the years (80). The ayurveda system was formally introduced to Sri Lanka from north India along with Buddhism during the period of King Devanampiyatissa (247-207 B.C.) (82). Nevertheless, the indigenous traditional medicine system had been treating the sick in a developed manner long before the ayurveda system was introduced to Sri Lanka.

The colonial conquests of Sri Lankan territory started in 1505 A.D. with the Portuguese arriving in Sri Lanka. The settlers reportedly used local knowledge to cure dysentery and snake poisoning among soldiers. Thereafter, the Dutch who ruled Sri Lanka from 1640 to 1796 A.D. built many hospitals in the country where herbal medicines were used alongside drugs imported from Europe. During this period, King Naredrasinghe (1707 A.D.) translated a 13th century palm manuscript on medicine ("Bhesajja Manjusa") and also compiled a book on indigenous medicinal prescriptions ("Vattoru Vedapotha"). The British colonial period started in 1796. The Sri Lankan traditional medicine system faced a significant decline during the British colonial era wherein Western medicine was established. Today, western medicine is the dominant form of treatment used in Sri Lanka, especially among the urban population (83). A notable exception to this trend under the British rule, was the establishment of a state-sponsored college of indigenous medicine in 1929 (currently called the Institute of Indigenous Medicine, a center for study and research on the traditional medicine system). It is important that this rich traditional medicine system is preserved in Sri Lanka alongside the western medicine system and that it should not be diminished with the current tempo of globalization (74). The ministry of health, nutrition and indigenous medicine of Sri Lanka is working on integrating the modern western medicine system with the traditional medicine practice along with enhancing standardization. This is in accord with the WHO 2014-2023 traditional medicine strategy, aimed at strengthening the role of traditional medicine in keeping populations healthy. Furthermore, traditional medicine could be used in diseases for which there is no treatment by modern medicine, and traditional medicine can also be used as an adjuvant therapy to improve quality of life. Currently, there are around 20,353 registered Ayurvedic physicians and 8,000 indigenous traditional medicine practitioners who are engaged in public healthcare in Sri Lanka (68).

The global wellness market is currently valued at ~ 4.2 trillion USD, of which ~ 360 billion USD comprises traditional and complementary medicine. This demonstrates that Sri Lanka has a vast economic potential with its traditional medicine system in disease prevention, diagnosis and management, and also in the development of standardized products that are safe and effective, using modern-day science and technology. As such, Sri Lanka should not be a country just providing the raw materials of natural products but should be a country developing new products with the help of local as well as foreign

collaborators. This would place Sri Lanka on the world map for innovation in wellness medication. It is also worth noting that the Sri Lankan traditional medicinal system has not received as much attention as the Indian ayurveda medicinal system. Therefore, comprehensive studies on its therapeutic potential using modern-day science and technology will be vital in demonstrating its importance to the world (71) (84). It should be noted that only ~ 1% of Sri Lankan plants and traditional medicinal formulae have been scientifically evaluated, possibly due to insufficient resources. The island is emerging as a leading destination for wellness tourism due to its rich cultural and wellness lifestyle-based heritage. In this context, it is important to scientifically validate and determine the mechanisms of action of some of the medications used for complicated etiologies such as cancer with the aim of personalizing medicine according to the patient's need. Personalized medicine helps in the identification of the precise cause and therapeutic target at different stages in the disease process. Thus, researchers involved in modern drug discovery should start revisiting ancient traditional medicine knowledge of the country and conduct research on Sri Lankan prodigious plant sources when developing new effective pharmacological agents to treat complex diseases such as cancer.

2.5. Cytotoxic activity of plants from Sri Lanka

The incidence of cancer is increasing globally including in Sri Lanka. This could be due to aging of the population and adoption of various lifestyle factors such as westernized diets, smoking, consumption of alcohol and lack of physical activity (85-86). Cancer is a multifactorial disease and it is generally difficult to treat, especially at advanced stages. Further, resistance to cancer chemotherapy is a common phenomenon. We have not yet been able to conquer cancer with the currently available therapies. Therefore, clearly, novel pharmaceuticals are needed to combat cancer and development of anticancer therapies from natural products remains crucial (87-89). Among the many medicinal properties that Sri Lankan plants possess, cytotoxic/antiproliferative activity has been documented and might be useful when developing novel agents for cancer. The cytotoxic/antiproliferative activity of preparations of Sri Lankan plant extracts are listed in Table 1.

Organic extracts from some of the plant species listed in Table 1 contain several active chemical compounds that have cytotoxic/ antiproliferative activity according to researchers in Sri Lanka. It is essential to identify active compounds from plants so that they can be tested for therapeutic potential. Table 2 lists some of the active compounds isolated from these plant extracts. A few of these compounds are novel and some are already in use. The listed compounds which are already in use are currently used as food/dietary supplements and generally considered as safe in terms of disease treatment and/or prevention. However, it should be noted that the Food and Drug Administration (FDA) and European Food Safety Authority (EFSA) do not approve food supplements before they are marketed. It is the responsibility of the manufacturers and distributors to make sure that the dietary products are safe before they go to the market. The consumer could also consult a healthcare professional before using any food supplements for their own safety (102-103). The listed compounds are promising and warrant continued investigation both at cellular and clinical level with the aim of developing pharmaceutical agents for various complicated etiologies such as cancer.

3. CONCLUSIONS

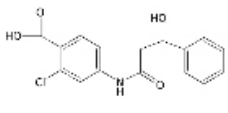
HTS and combinatorial chemistry play a major role in the drug discovery industry today. A multidisciplinary approach to drug discovery involving these methods combined with natural product drug discovery will be a good approach to combat the current decline in the exploration of natural products for novel compounds (121). Indeed, the exploration of nature is vital in finding novel active compounds and leads for various human diseases and this exploration should not be allowed to diminish (122). Scientists in developing countries such as Sri Lanka, where natural products are available in abundance, should take the lead and implement interdisciplinary research on natural products together with traditional medical practitioners, healthcare professionals of modern medicine, academics and industrialists. This would contribute to the globally growing pharmaceutical discovery and drug development. A multi-disciplinary approach will also help to pave the way for Sri Lanka to burrow in the goldmine of the global wellness market. Furthermore, traditional medicine should be scientifically evaluated at a molecular level which will help to determine the mechanism of action. Moreover, determination of safety and efficacy of the treatment at a clinical level, especially in the case of complex diseases such as cancer, will make the medicines more promising in the era of precision medicine. The use of technologies, such as nanotechnology, would also be helpful in the formulation of traditional medicines with improved bioavailability and efficacy in the treatment of cancer, although additional scientific investigations may be needed. Additionally, a thought should be given to maintaining a systematic database in Sri Lanka, documenting research conducted on the island's natural products, thus providing a very valuable resource for researchers around the globe.

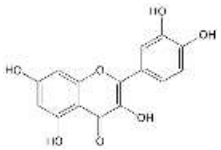
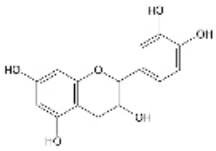
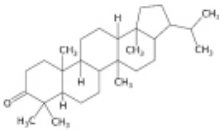
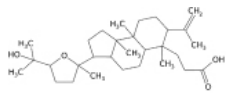
Table 1. Plants from Sri Lanka with cytotoxic and antiproliferative properties

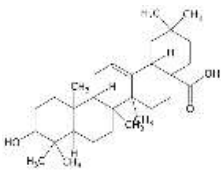
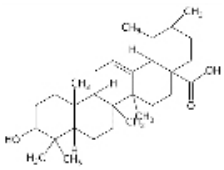
Name of plant/s	Family	Local names used in Sri Lanka	Biologically active plant extracts	*In vitro* cytotoxicity/antiproliferative activity in cancer cell lines
Mangifera zeylanica	Anacardiaceae	(Sinhalese name (S))- Etamba, (Tamil name (T))- Kaddu-ma	Hexane extract of bark, Chloroform extract of bark and Chloroform extract of fruit peel	Hexane extract of bark- MCF7 breast cancer cells, MDA-MB 231 breast cancer cells and SKOV3 ovarian cancer cells. Chloroform extract of bark- MDA-MB 231 breast cancer cells (90). Chloroform extract of fruit peel- MCF7 breast cancer cells (91).
Flueggea leucopyrus	Phyllanthaceae	S-Heen Katupila, T-Mudpulanti	Aqueous decoction of leaves	Hep-2 cervical cancer cells and AN3CA endometrium cancer cells (92-93).
Scyphiphora hydrophyllacea	Rubiaceae	S-Kadolana species, T-Sathuppunila thawarankal species	Hexane extract of leaves and Chloroform extract of leaves	Hexane and chloroform extracts- HepG2 liver cancer cells (94).
Mangifera indica	Anacardiaceae	S-Ambha, T-Manga	Methanol extract of bark	MCF7 breast cancer cells, MDA-MB 231 breast cancer cells and SKOV3 ovarian cancer cells (95).
Phyllanthus debilis	Phyllanthaceae	S-Elapitawakka, T-Kulhainelli	Aqueous decoction of roots	RD rhabdomyosarcoma cells (96).
Campnosperma zeylanica	Anacardiaceae	S-Aridda	Hexane extract of leaves and bark	Hexane extract of leaves and bark- MCF7 and MDA-MB 231 breast cancer cells (69).
Bhesa ceylanica	Centroplacaceae	S-Eth heraliya, T-Konnai	Ethyl acetate extract of bark	MCF7 cells and MDA-MB 231 breast cancer cells (69).
Calophyllum calaba	Clusiaceae	S-Guru keena, T-Chirupunnai	Chloroform extract of leaves and ethyl acetate extract of leaves	Chloroform extract of leaves and ethyl acetate extract of leaves - MCF7 breast cancer cells (69).
Calophyllum moonii	Clusiaceae	S-Domba keena, T-Punnai	Methanol extract of leaves and ethyl acetate extract of leaves	Methanol extract of leaves- MCF7 and MDA-MB 231 breast cancer cells. Ethyl acetate extract of leaves- MCF7 breast cancer cells (69).
Calophyllum tomentosum	Clusiaceae	S-Tel keena, T-Pongu	Chloroform extract of bark	MCF7 breast cancer cells (69).
Connarus championii	Connaraceae	S-Wel radaliya	Hexane extract of leaves and chloroform extract of leaves	Hexane extract of leaves- MCF7 and MDA-MB 231 breast cancer cells. Chloroform extract- MDA-231 breast cancer cells (69).
Schumacheria castaneifolia	Dilleniaceae	S-Kekiriwara	Ethyl acetate extract of bark and chloroform extract of bark	Ethyl acetate extract of bark and chloroform extract of bark- MDA-MB 231 breast cancer cells (69).
Doona macrophylla	Dipterocarpaceae	S-Maha beraliya	Methanol extract of bark	MCF7 breast cancer cells (69).
Chaetocarpus coriaceus	Peraceae	S-Gal hadoka	Methanol extract of bark	MCF7 breast cancer cells (69).
Lijndenia capitellata	Melastomaceae	S-Pini baru,	Ethyl acetate extract of leaves	MCF7 breast cancer cells (69).
Memecylon rostratum	Melastomaceae	S-Heen kuratiya	Hexane extract of bark	MCF7 breast cancer cells (69).
Cleistocalyx nervosum	Myrtaceae	S-Bata damba	Methanol extracts of leaves and bark and Ethyl acetate extracts of leaves and bark	Methanol and ethyl acetate extracts of leaves- MDA-MB 231 breast cancer cells Methanol and ethyl acetate extracts of bark- MCF7 breast cancer cells (69)
Ochna jabotapita	Ochnaceae	S-Mal kera, T-Chilanti	Chloroform extract of leaves	MCF7 breast cancer cells (69).
Gardenia crameri	Rubiaceae	S-Galis	Ethyl acetate extract of bark	MCF7 breast cancer cells (69).

Tabernaemontana divaricata	Apocynaceae	S-Wathusudda, T-Nandi-battai	Ethanol extract of leaves and stem	Ethanol extract of leaves and stem- SKBR3 breast cancer cells (97).
Plumeria rubra	Apocynaceae	S-Araliya, T-Arali	Ethanol extract of leaves	SKBR3 breast cancer cells (98).
A traditional medicine formulation of *Adenanthera pavonina* and *Thespesia populnea*	Fabaceae (*Adenanthera pavonina*), Malvaceae (Thespesia populnea)	S-Madatiya, T-Anaikuntumani (*Adenanthera pavonina*), S-Gansuriya, T-Kavarachu (Thespesia populnea)	Aqueous decoction of equal amounts of bark of both plants	Hep-2 cervical cancer cells (99).
A traditional medicine formulation of *Nigella sativa, Hemidesmus indicus* and *Smilax glabra*	Ranunculaceae (*Nigella sativa*), Apocynaceae (*Hemidesmus indicus*), Smilacaceae (*Smilax glabra*)	S-Kalu duru, T- Karum-cheerakam (*Nigella sativa*), S-Iramusu, T-Nannari (*Hemidesmus indicus*), S-Cheena ala (*Smilax glabra*)	Aqueous decoction of equal amounts of *Nigella sativa* seeds, *Hemidesmus indicus* roots and *Smilax glabra* rhizomes	HepG2 liver cancer cells (100).
A traditional medicine formulation of *Terminalia bellirica, Terminalia chebula, Phyllanthus emblica* and *Commiphora Mukul* and a traditional medicine formulae of *Terminalia bellirica, Terminalia chebula, Phyllanthus emblica, Commiphora mukul, Smilax china* and *Nigella sativa*	Combretaceae (*Terminalia bellirica*), Combretaceae (*Terminalia chebula*), Phyllanthaceae (*Phyllanthus emblica*), Burseraceae (*Commiphora Mukul*), Smilacaceae (*Smilax china*) and Ranunculaceae (*Nigella sativa*)	S-Bulu, T-Ahdan-koddai (*Terminalia bellirica*), S-Aralu, T-Kadukkay (*Terminalia chebula*), S-Nelli, T-Topu-nelli (*Phyllanthus emblica*), S-Gugul (*Commiphora Mukul*), S-Cheena ala (*Smilax china*) and S-Kalu duru, T- Karum-cheerakam (*Nigella sativa*)	Aqueous decoction of equal amounts of *Terminalia bellirica* fruit, *Terminalia chebula* fruit, *Phyllanthus emblica* fruit and *Commiphora mukul* resin (decoction 1) and the second aqueous decoction contained equal amounts of *Terminalia bellirica* fruit, *Terminalia chebula* fruit, *Phyllanthus emblica* fruit, *Commiphora mukul* resin, *Smilax china* root and *Nigella sativa* seeds (decoction 2).	Decoction 1 and 2- RD rhabdomyosarcoma cells (101).

Table 2. Chemical compounds isolated from medicinal plant species from Sri Lanka

Plant	Extract	Compound/s	Structure	In vitro Cytotoxicity/ antiproliferative activity in cancer cell lines	In vivo activity and activity in human clinical trials if performed	Names of pharmaceutical drugs developed if any with the compound/s
Mangifera zeylanica	Hexane extract of bark	A resorcinolic lipid-5-((8Z, 11Z, 14Z)-hexatriaconta-8, 11, 14-trienyl) benzene-1,3-diol		MCF7 breast cancer cells (104).	None.	None. If a therapy is developed it could have anticancer effects on hormone positive breast cancer.
	Chloroform extract of bark	Chloromangiferamide		MDA-MB 231 breast cancer cells (105).	None.	None. If a therapy is developed it could have anticancer effects on triple negative breast cancer.

		Quercetin		MDA-MB 231, MCF7 breast cancer cells and SKOV3 ovarian cancer cells (105).	Quercetin has shown anticancer effects in a variety of cancers for example it has shown to reduce tumor volume of MCF7 tumor mouse models (106-107). Quercetin has also shown inhibitory effects against tyrosine kinase in a phase I clinical trial with cancer patients (108).	Quercetin is currently sold as a food supplement around the world for various ailments such as seasonal allergies, for the prevention of diabetic cataracts, for chronic prostatitis, and as an adjunctive therapy in cancer (109).
		Catechin		MDA-MB 231, MCF7 breast cancer cells and SKOV3 ovarian cancer cells (105).	Catechin has shown to have an effect on a variety of cancers for example, it was shown to reduce lung metastasis induced by B16F-10 murine melanoma cells in mice (110). Further, catechins in green tea were shown to reduce high-grade prostate intraepithelial neoplasia before prostate cancer develops in men (111).	Catechin is found in food supplements which are sold currently worldwide such as green tea catechins. These have shown to be beneficial in cancer, cardiovascular disease, diabetes, obesity, infections and neurological diseases (112).
Scyphiphora hydrophyllacea	Hexane extract of leaves	Hopenone-I		HepG2 liver cancer cells, MCF7 breast cancer cells and AN3CA endometrium cancer cells (113).	None.	None. If a therapy is developed it could have anticancer effects on hormone positive breast cancer, hepatocellular carcinoma and endometrium cancer.
		Eichlerianic acid		MCF7 breast cancer cells and NCI-H292 lung cancer cells (114).	None.	None. If a therapy is developed it could have anticancer effects on hormone positive breast cancer, and in mucoepidermoid carcinoma.

	Chloroform extract of leaves	Oleanolic acid		MCF7 breast cancer cells and NCI-H292 lung cancer cells (114).	Oleanolic acid was shown to reduce tumor growth in PC-3 (human prostate cancer) tumor mouse models (115). This compound has shown satifactory results in human clinical trials, thus it is used to treat human liver diseases such as hepatitis in China (116).	Oleanolic acid can be found in food supplements globally and it might be benefical in cancer, diabetes, infections, liver diseases, cardiovascular disease, and inflammation (117).
		Ursolic acid		MCF7 breast cancer cells and NCI-H292 lung cancer cells (114).	Ursolic acid has shown anticancer effects in a variety of cancers, for example it has reduced tumor size in MMTV-Wnt-1 (mammary) mouse models (118).	Ursolic acid can be found in food supplements worldwide and it could be benefical in cancer, inflammation, and in ageing skin (119).
Campnosperma zeylanica	Hexane extract of leaves	Campnospermenone A		MCF-7 and MDA-MB 231 breast cancer cells (120).	None.	None. If a therapy is developed it could have anticancer effects on hormone positive and triple negative breast cancers.
		Campnospermenone B		MCF-7 and MDA-MB 231 breast cancer cells (120).	None.	Same as for campnospermenone A.
		Campnospermenone C		MCF-7 and MDA-MB 231 breast cancer cells (120).	None.	Same as for campnospermenone A..

4. REFERENCES

1. A L Harvey: Natural products in drug discovery. *Drug Discov. Today*, 13, 894-901 (2008) DOI: 10.1016/j.drudis.2008.07.004

2. C Veeresham: Natural products derived from plants as a source of drugs. *J Adv Pharm Technol Res*, 4, 200-201 (2012) DOI: 10.4103/2231-4040.104709

3. J W H Li, J C Vederas: Drug discovery and natural products: end of an era or an endless frontier? *Science*, 325, 161-165 (2009) DOI: 10.1126/science.1168243

4. M J Balunas, A D Kinghorn: Drug discovery from medicinal plants. *Life Sci.*, 78, 431-441 (2005) DOI: 10.1016/j.lfs.2005.09.012

5. D J Newman, G M Cragg, K M Snader: The influence of natural products upon drug discovery. *Nat. Prod. Rep*, 17, 215-234 (2000) DOI: 10.1039/a902202c

6. J G Mahdi: Medicinal potential of willow: A chemical perspective of aspirin discovery. *J. Saudi Chem. Soc*, 14, 317-322 (2010) DOI: 10.1016/j.jscs.2010.04.010

7. F E Koehn, G T Carter: The evolving role of natural products in drug discovery. *Nat Rev Drug Discov.,* 4, 206-220 (2005) https://doi.org/10.1038/nrd1657

8. K S Lam: New aspects of natural products in drug discovery. *Trends Microbiol*, 15, 279-289 (2007) DOI: 10.1016/j.tim.2007.04.001

9. M Pascolutti, R J Quinn: Natural products as lead structures: chemical transformations to create lead-like libraries. *Drug Discov Today*, 19, 215-221 (2014) DOI: 10.1016/j.drudis.2013.10.013

10. D J Newman, G M Cragg: Natural products as sources of new drugs from 1981 to 2014. *J. Nat. Prod*, 79, 629-661 (2016) DOI: 10.1021/acs.jnatprod.5b01055

11. A L Harvey, R Edrada-Ebel, R J Quinn: The re-emergence of natural products for drug discovery in the genomics era. *Nat. Rev. Drug Discov.*, 14, 111-129 (2015) DOI: 10.1038/nrd4510

12. J Clardy, C Walsh: Lessons from natural molecules. *Nature*, 432, 829-837 (2004) DOI: 10.1038/nature03194

13. Y Luo, R E Cobb, H Zhao: Recent advances in natural product discovery. *Curr Opin Biotechnol*, 30, 230-237 (2014) DOI: 10.1016/j.copbio.2014.09.002

14. D J Newman: Natural products as leads to potential drugs: an old process or the new hope for drug discovery? *J. Med. Chem.,* 51, 2589-2599 (2008) DOI: 10.1021/jm0704090

15. D J Newman, G M Cragg: Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod*, 70, 461-477 (2007) DOI: 10.1021/np068054v

16. V Brower: Back to nature: extinction of medicinal plants threatens drug discovery. *J. Natl. Cancer Inst.*, 100, 838-839 (2008) DOI: 10.1093/jnci/djn199

17. M S Butler: The role of natural product chemistry in drug discovery. *J. Nat. Prod.*, 67, 2141-2153 (2004) DOI: 10.1021/np040106y

18. B Shen: A new golden age of natural products drug discovery. *Cell*, 163, 1297-1300 (2015) DOI: 10.1016/j.cell.2015.11.031

19. Y Ding, C Ding, N Ye, Z Liu, E A Wold, H Chen, C Wild, Q Shen, J Zhou: Discovery and development of natural product oridonin-inspired anticancer agents. *Eur. J. Med. Chem*., 122, 102-117 (2016) DOI: 10.1016/j.ejmech.2016.06.015

20. D A Dias, S Urban, U Roessner: A historical overview of natural products in drug discovery. *Metabolites*, 2, 303–336 (2012) DOI: 10.3390/metabo2020303

21. Y Chin, M J Balunas, H B Chai, A D Kinghorn: Drug discovery from natural sources. *AAPS J.,* 8, 239-253 (2006) DOI: 10.1007/BF02854894

22. M J Stone, D H Williams: On the evolution of functional secondary metabolites (natural products) *Mol Microbiol*., 6, 29-34 (1992) DOI: 10.1111/j.1365-2958.1992.tb00834.x

23. Z Guon: The modification of natural products for medical use. *Acta Pharm Sin B.*, 2, 119-136 (2017)

24. N S Yarla, A Bishayee, G Sethi, P Reddanna, A M Kalle, B L Dhananjaya, K S Dowluru, R Chintala, G R Duddukuri: Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. *Semin Cancer Biol.*, 40, 48-81 (2016) DOI: 10.1016/j.semcancer.2016.02.001

25. T F Molinski, D S Dalisay, S L Lievens, J P Saludes: Drug development from marine natural products. *Nat Rev Drug Discov.*, 8, 69-85 (2009) DOI: 10.1038/nrd2487

26. V A Stonik: Marine natural products: a way to new drugs. *Acta Naturae*,, 2, 15-25 (2009)

27. T L Simmons, E Andrianasolo, K McPhail, P Flatt, W H Gerwick: Marine natural products as anticancer drugs. *Mol Cancer Ther.,* 4, 333-342 (2005)

28. K Senthilkumar, S Kim: Marine invertebrate natural products for anti-inflammatory and chronic diseases. *Evid Based Complement Alternat Med*, 2013, (2013) DOI: 10.1155/2013/572859

29. D J Faulkner: Marine natural products. *Nat. Prod. Rep*, 18, 1-49 (2001) DOI: 10.1039/b006897g

30. M J Abad, P Bermejo: Bioactive natural products from marine sources. Studies in *Natural Products Chemistry*, 25, 683-755 (2001) DOI: 10.1016/S1572-5995(01)80021-1

31. P Vuorela, M Leinonen, P Saikku, P Tammela, J P. Rauhad, T Wennberge, H Vuorela: Natural products in the process of finding new drug candidates. *Curr Med Chem*., 11, 1375-1389 (2004)
DOI: 10.2174/0929867043365116

32. E M El-Hossary, C Cheng, M M Hamed, A N El-Sayed Hamed, K Ohlsen, U Hentschel, U R Abdelmohsen: Antifungal potential of marine natural products. Eur. *J. Med. Chem.,* 126, 631-651 (2017)
DOI: 10.1016/j.ejmech.2016.11.022

33. H Luesch, R Montaser: Marine natural products: a new wave of drugs? *Future Med Chem*., 12, 1475-1489 (2011)

34. J W Blunt, B R Copp, W Hu, M H G Munro, P T Northcote, M R Prinsep: Marine natural products. *Nat. Prod. Rep.,* 26, 170-244 (2009)
DOI: 10.1039/b805113p

35. J W Blunt, B R Copp, M H G Munro, P T Northcote, M R Prinsep: Marine natural products. *Nat. Prod. Rep*., 26, 165-237 (2010)
DOI: 10.1039/b906091j

36. G M Cragg, D J Newman: Natural products: A continuing source of novel drug leads. *Biochim. Biophys. Acta*,, 1830, 3670-3695 (2013)
DOI: 10.1016/j.bbagen.2013.02.008

37. B Haefner: Drugs from the deep: marine natural products as drug candidates. *Drug Discov Today,* 8, 536-544 (2003)
DOI: 10.1016/S1359-6446(03)02713-2

38. M F Vicente, A Basilio, A Cabello, F Pela´ez: Microbial natural products as a source of antifungals. *Clin. Microbiol.Infect,.* 9, 15-32 (2003)
DOI: 10.1046/j.1469-0691.2003.00489.x

39. A A L Gunatilaka, E M K Wijeratne: Natural products from bacteria and fungi, *Phytochemistry and Pharmacognosy*. 1-10 (2010)

40. L Townsley, E A Shank: Natural-product antibiotics: cues for modulating bacterial biofilm formation. *Trends Microbiol*., 17, 1-11 (2017)
DOI: 10.1016/j.tim.2017.06.003

41. M R Wilson, L Zha, E P Balskus: Natural product discovery from the human microbiome. *J. Biol. Chem*., 292, 8546-8552 (2017)
DOI: 10.1074/jbc.R116.762906

42. E T Hillman, L R Readnour, K V Solomon: Exploiting the natural product potential of fungi with integrated- omics and synthetic biology approaches. *Curr Opin Syst Biol*, 5, 50-56 (2017)
DOI: 10.1016/j.coisb.2017.07.010

43. V L Challinor, H B Bode: Bioactive natural products from novel microbial sources. *Ann. N. Y. Acad. Sci.*, 1354, 82-97 (2015)
DOI: 10.1111/nyas.12954

44. M. G. Moloney: Natural products as a source for novel antibiotics. *Trends Pharmacol. Sci.,* 37, 689-701 (2016)
DOI: 10.1016/j.tips.2016.05.001

45. G M Cragg, D J Newman: Natural product drug discovery in the next millennium. *Pharm. Biol.,* 39, 8-17 (2011)

46. J Cortes, J Baselga: Targeting the microtubules in breast cancer beyond taxanes: The epothilones. *Oncologist*, 12, 271-280 (2007)
DOI: 10.1634/theoncologist.12-3-271

47. L Katz, R H. Baltz: Natural product discovery: past, present, and future. *J. Ind. Microbiol. Biotechnol*., 43, 155-176 (2016)
DOI: 10.1007/s10295-015-1723-5

48. I Raskin, D M Ribnicky, S Komarnytsky, N Ilic, A Poulev, N Borisjuk, A Brinker, D A Moreno, C Ripoll, N Yakoby, J M.O'Neal, T Cornwell, I Pastor, B Fridlender: Plants and human health in the twenty-first century. *Trends Biotechnol*., 20, 522-531 (2002)
DOI: 10.1016/S0167-7799(02)02080-2

49. R A Dixon: Natural products and plant disease resistance. *Nature*, 411, 843-847 (2001)
DOI: 10.1038/35081178

50. J Mann: Natural products in cancer chemotherapy: past, present and future. *Nat. Rev. Cancer*., 2, 143-148 (2002)
DOI: 10.1038/nrc723

51. G M Cragg, D J Newman: Plants as a source of anti-cancer agents. *J. Ethnopharmacol*., 100, 72-79 (2005)
DOI: 10.1016/j.jep.2005.05.011

52. A Kumar, D Patil, P R Rajamohanan, A Ahmad: Isolation, purification and characterization of vinblastine and vincristine from endophytic fungus fusarium oxysporum isolated from Catharanthus roseus. *PLoS One*, 8, e71805 (2013)
DOI: 10.1371/journal.pone.0071805

53. Q Yue, X Liu, D Gu: Microtubule-binding natural products for cancer therapy. *Planta Med.*, 76, 1037–1043 (2010)
DOI: 10.1055/s-0030-1250073

54. L F Tietze, H P Bell, S Chandrasekhar: Natural product hybrids as new leads for drug discovery. *Angew Chem Int Ed Engl.*, 42, 3996-4028 (2003)
DOI: 10.1002/anie.200200553

55. A M Clark: Natural products as a resource for new drugs. *Pharm Res*, 13, 1133-1141 (1996)
DOI: 10.1023/A:1016091631721

56. M Moudi, R Go, C Y S Yien, M Nazre: Vinca Alkaloids. *Int J Prev Med.*, 4, 1231–1235 (2013)

57. K A Lyseng-Williamson, C Fenton: Docetaxel A review of its use in metastatic breast cancer. *Drugs*, 65, 2513-2531 (2005)
DOI: 10.2165/00003495-200565170-00007

58. G B Maru, R R Hudlikar, G Kumar, K Gandhi, M B Mahimkar: Understanding the molecular mechanisms of cancer prevention by dietary phytochemicals: From experimental models to clinical trials. *World J Biol Chem.*, 26, 88-99 (2016)
DOI: 10.4331/wjbc.v7.i1.88

59. H Greenlee: Natural products for cancer prevention. *Semin Oncol Nurs*, 28, 29-44 (2012)
DOI: 10.1016/j.soncn.2011.11.004

60. D Sinha, N Sarkar, J Biswas, A Bishayee: Resveratrol for breast cancer prevention and therapy: Preclinical evidence and molecular mechanisms. *Semin. Cancer Biol.*, 40, 209-232 (2016)
DOI: 10.1016/j.semcancer.2015.11.001

61. L Reddy, B Odhav K D Bhoola: Natural products for cancer prevention: a global perspective. *Pharmacol. Ther.*, 99, 1-13 (2003)
DOI: 10.1016/S0163-7258(03)00042-1

62. K Lee: Discovery and development of natural product-derived chemotherapeutic agents based on a medicinal chemistry approach. *J. Nat. Prod.,* 73, 500-516 (2010)
DOI: 10.1021/np900821e

63. H Wang, T O Khor, L Shu, Z Su, F Fuentes, J Lee, A T Kong: Plants against cancer: a review on natural phytochemicals in preventing and treating cancers and their druggability. *Anticancer Agents Med Chem*, 12, 1281-1305 (2012)
DOI: 10.2174/187152012803833026

64. A R M R Amin, O Kucuk, F R Khuri, D M Shin: Perspectives for cancer prevention with natural compounds. *J. Clin. Oncol.,* 27, 2712-2725 (2009)
DOI: 10.1200/JCO.2008.20.6235

65. K Sanders, Z Moran, Z Shi, R Paul, H Greenlee: Clinical update 2016: natural products for cancer prevention. *Semin Oncol Nurs.*, 32, 215-240 (2016)
DOI: 10.1016/j.soncn.2016.06.001

66. S L view: Floral Species found in Sri Lanka. (cited 04-08-2017); Available from: http://www.srilankaview.com/floraSL.htm.

67. J Russell-Smith, N S Karunaratne, R Mahindapala: Rapid inventory of wild medicinal plant populations in Sri Lanka. *Biol. Conserv.*, 132, 22-32 (2006)
DOI: 10.1016/j.biocon.2006.03.009

68. T N M Kankanamalage, R M Dharmadasa, D C Abeysinghe, R G S Wijesekara: A survey on medicinal materials used in traditional systems of medicine in Sri Lanka. *J Ethnopharmacol.*, 155, 679-691 (2014)
DOI: 10.1016/j.jep.2014.06.016

69. P P Jayarathna, K H Tennekoon, S R Samarakoon, I Thabrew, E H Karunanayake, E D De Silva, M K Ediriweera: Cytotoxic, antioxidant and apoptotic effects of twenty Sri Lankan endemic plants in breast cancer cells. *European J Med Plants*, 15, 1-15 (2016)
DOI: 10.9734/EJMP/2016/26591

70. L Travels, Flora and fauna in Sri Lanka. (cited 04-08-2017); Available from: https://lanka.com/about/interests/flora-fauna/.

71. V Y Waisundara, M I Watawana: The classification of Sri Lankan medicinal herbs:

an extensive comparison of the antioxidant activities. *J Tradit Complement Med*, 4, 196-202 (2014)
DOI: 10.4103/2225-4110.126175

72. P B Weragoda: The traditional system of medicine in Sri Lanka. *J Ethnopharmacol*., 2, 71-73 (1980)
DOI: 10.1016/0378-8741(80)90033-1

73. K Hettiarachchi: Surgery in an ancient kingdom. (cited 02-10-2017); Available from: http://www.sundaytimes.lk/111030/Plus/plus_01.html.

74. P Petitjean, C Jami, A M Moulin: Science and Empires. Vol. 136, 1992.
DOI: 10.1007/978-94-011-2594-9

75. S N Arseculeratne: Interactions between traditional medicine and 'western' medicine in Sri Lanka. *Soc. Sci*., 30, 4-17 (2002)

76. M S Muralitharan, S Chandler, T Coulepis, R Mitra: Medicinal Plants of Sri Lanka. *APBN*, 11, 183-186 (2007)

77. A Broom, K Wijewardena, D Sibbritt, J Adams, K R Nayar: The use of traditional, complementary and alternative medicine in Sri Lankan cancer care: Results from a survey of 500 cancer patients. *Public Health*, 124, 232-237 (2010)
DOI: 10.1016/j.puhe.2010.02.012

78. V L Sri Lanka. Traditional medicine in Sri Lanka. (cited 05-08-2017); Available from: http://www.lankalibrary.com/rit/ayurveda2.htm.

79. I Wolffers: Illness behavior in Sri Lanka: results of a survey in two sinhalese communities. *Soc Sci Med.*, 27, 545-552 (1988)
DOI: 10.1016/0277-9536(88)90378-4

80. M C Weerasinghe, D N Fernando: Paradox in treatment seeking: an experience from rural Sri Lanka. *Qual Health Res.,* 21, 365-372 (2011)
DOI: 10.1177/1049732310385009

81. A S U Colombo Deshiya Chikitsa. (cited 02-10-2017); Available from: http://iim.cmb.ac.lk/ayurveda-section/?department=deshiya-chikitsa.

82. I A A Medicine, IAAM Historical Perspective. (cited 03-10-2017); Available from: http://www.instituteofayurveda.org/english/history.htm.

83. R M Abeyrathne: The role played by the Ceylon reformed society and the oriental medical science fund in the revival of traditional medicine in Ceylon/Sri Lanka. *Social Affairs*., 1, 33-46 (2015)

84. R P Labadie: Problems and possibilities in the use of traditional drugs. *J Ethnopharmacol*., 15, 221-230 (1986)
DOI: 10.1016/0378-8741(86)90162-5

85. A Jemal, F Bray, M M Center, J Ferlay, E Ward, D Forman: Global cancer statistics. *CA Cancer J Clin*, 61, 69-90 (2011)
DOI: 10.3322/caac.20107

86. N C C Programme, Cancer incidence data Sri Lanka 2010. Vol. 1, 2010.

87. D A Yardley: Drug resistance and the role of combination chemotherapy in improving patient outcomes. *Int J Breast Cancer*, 2013, 1-15 (2013)
DOI: 10.1155/2013/137414

88. C Daniels, J Ramos, C Molina-Santiago, C Michán: Directed evolution, natural products for cancer chemotherapy, and micro-biosensing robots. *Microb Biotechnol.*, 4, 314-317 (2011)
DOI: 10.1111/j.1751-7915.2011.00267.x

89. Y Shu: Recent natural products based drug development: a pharmaceutical industry perspective. *J. Nat. Prod*., 61, 1053-1071 (1998)
DOI: 10.1021/np9800102

90. M K Ediriweera, K H Tennekoon, S R Samarakoon, I thabrew, E D De Silva: A study of the potential anticancer activity of *Mangifera zeylanica* bark: Evaluation of cytotoxic and apoptotic effects of the hexane extract and bioassay-guided fractionation to identify phytochemical constituents. *Oncol. Lett*., 11, 1335-1344 (2016)
DOI: 10.3892/ol.2016.4087

91. M K Ediriweera, K H Tennekoon, S R Samarakoon, I Thabrew, E D De Silva: Induction of apoptosis in MCF-7 breast cancer cells By Sri Lankan endemic mango (*Mangifera zeylanica*) Fruit peel through oxidative stress and analysis of its phytochemical constituents. *J. Food Biochem*., 41, e12294 (2016)
DOI: 10.1111/jfbc.12294

92. P Soysa, I S De Silva, J Wijayabandara: Evaluation of antioxidant and antiproliferative activity of *Flueggea leucopyrus* Willd

(katupila) *BMC Complement Altern Med*., 14, 274 (2014)
DOI: 10.1186/1472-6882-14-274

93. S R Samarakoon, S B Kotigala, I Gammana-Liyanage, I Thabrew, K H Tennekoon, A Siriwardana, P B Galhena: Cytotoxic and apoptotic effect of the decoction of the aerial parts of *Flueggea leucopyrus* on human endometrial carcinoma (AN3CA) cells. *Trop J Pharm Res*., 13, 873-880 (2014)
DOI: 10.4314/tjpr.v13i6.7

94. S R Samarakoon, C Shanmuganathan, M K Ediriweera, P Piyathilaka, K H Tennekoon, I Thabrew, P B Galhena, E D De Silva: Anti-hepatocarcinogenic and anti-oxidant effects of mangrove plant Scyphiphora hydrophyllacea. *Pharmacogn Mag*., 13, 76-83 (2017)
DOI: 10.4103/0973-1296.203989

95. M K Ediriweera, K H Tennekoon, S R Samarakoon, I Thabrew, E D De Silva: Cytotoxic and apoptotic effects of the bark of two common mango (*Mangifera indica*) varieties from Sri Lanka on breast and ovarian cancer cells. *Br J Pharm Res.*, 10, 1-7 (2016)
DOI: 10.9734/BJPR/2016/24004

96. D Perera, P Soysa, S Wijeratne: Polyphenols contribute to the antioxidant and antiproliferative activity of *Phyllanthus debilis* plant in-vitro. *BMC Complement Altern Med.*, 16, 339 (2016)
DOI: 10.1186/s12906-016-1324-5

97. A I Kuruppu, M Al-Hayali, L Zhang, C Parmenter, N Weston, L Turyanska, T D Bradshaw: *Tabernaemontana divaricate* illustrating potent anticancer activity in HER2 positive SKBR3 breast cancer cells, *TradMed international conference Colombo, Sri Lanka*, 1, 114 (2017)

98. A I Kuruppu, M Al-Hayali, L Zhang, L Turyanska, T D Bradshaw: A study on the potential anticancer activity of *Plumeria rubra*. *TradMed international conference Colombo, Sri Lanka*, 1, 123 (2017)

99. I K S Lindamulage, P Soysa: Evaluation of anticancer properties of a decoction containing *Adenanthera pavonina* L. and *Thespesia populnea* L. *BMC Complement Altern Med*., 16, 70 (2016)
DOI: 10.1186/s12906-016-1053-9

100. S R Samarakoon, I Thabrew, P B Galhena, K H Tennekoon: Modulation of apoptosis in human hepatocellular carcinoma (HepG2 cells) by a standardized herbal decoction of *Nigella sativa* seeds, *Hemidesmus indicus* roots and *Smilax glabra* rhizomes with anti-hepatocarcinogenic effects. *BMC Complement Altern Med*., 12, 25 (2012)
DOI: 10.1186/1472-6882-12-25

101. M G A N Perera, S S S B D P Soysa, D T U Abeytunga, R Ramesh: Antioxidant and cytotoxic properties of three traditional decoctions used for the treatment of cancer in Sri Lanka. *Pharmacogn Mag*., 4, 172-181 (2008)

102. U S Department of Health and Human Services, Dietary Supplements: What You Need to Know. (cited 01-10-2018); Available from: https://www.fda.gov/food/dietarysupplements/usingdietarysupplements/ucm109760.htm.

103. European Food Safety Authority, Food supplements. (cited 02-10-2018); Available from: https://www.efsa.europa.eu/en/topics/topic/food-supplements.

104. M K Ediriweera, K H Tennekoon, S R Samarakoon, A Adhikari, I Thabrewa, E D De Silva: Isolation of a new resorcinolic lipid from *Mangifera zeylanica* Hook.f.bark and its cytotoxic and apoptotic potential. *Biomed. Pharmacother*., 89, 194-200 (2017)
DOI: 10.1016/j.biopha.2017.01.176

105. M K Ediriweera, K H Tennekoon, A Adhikari, S R Samarakoon, I Thabrew, E D De Silva: New halogenated constituents from *Mangifera zeylanica* Hook.f. and their potential anti-cancer effects in breast and ovarian cancer cells. *J Ethnopharmacol.*, 189, 165-174 (2016)
DOI: 10.1016/j.jep.2016.05.047

106. M Hashemzaei, A D Far, A Yari, R E Heravi, K Tabrizian, S M Taghdisi, S E Sadegh, K Tsarouhas, D Kouretas, G Tzanakakis, D Nikitovic, N Y Anisimov, D A Spandidos, A M Tsatsakis, R Rezaee: Anticancer and apoptosis-inducing effects of quercetin *in vitro* and *in vivo*. *Oncol. Rep*., 38, 819-828 (2017)
DOI: 10.3892/or.2017.5766

107. Y Lee, J Shin, W S Lee, H G Lee, J Hwang, O J Park: Inhibitory properties of tumor

growth by quercetin in xenograft models. *Cancer Prev. Res*., 14, 54-59 (2009)

108. D R Ferry, A Smith, J Malkhandi, D W Fyfe, P G deTakats, D Anderson, J Baker, D J Kerr: Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition. *Clin. Cancer Res*., 2, 659-668 (1996)

109. WebMD, Medscape-Quercetin (Herbs/ Suppl) (cited 01-10-2018); Available from: https://reference.medscape.com/drug/quercetin-344495#2.

110. L G Menon, R Kuttan, G Kuttan: Anti-metastatic activity of curcumin and catechin. *Cancer Lett*., 141, 159-165 (1999) DOI: 10.1016/S0304-3835(99)00098-1

111. S Bettuzzi, M Brausi, F Rizzi, G Castagnetti, G Peracchia, A Corti: Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res*., 66, 1234-1240 (2006) DOI: 10.1158/0008-5472.CAN-05-1145

112. W C Reygaert: Green tea catechins: their use in treating and preventing infectious diseases. *BioMed Res. Int*., 2018, 1-9 (2018) DOI: 10.1155/2018/9105261

113. S R Samarakoon, N Fernando, M K Ediriweera, A Adhikari, L Wijayabandara, E D De Silva, K H Tennekoon: Isolation of Hopenone-I from the leaves of mangrove plant *Scyphiphora hydrophyllacea* and its cytotoxic properties. *Br J Pharm Res.*, 10, 1-6 (2016) DOI: 10.9734/BJPR/2016/23317

114. S R Samarakoon, M K Ediriweera, L Wijayabandara, N Fernando, L Tharmarajah, K H Tennekoon, P Piyathilaka, A Adhikari: Isolation of cytotoxic triterpenes from the mangrove plant, *Scyphiphora hydrophyllacea* C.F.Gaertn (Rubiaceae). *Trop J Pharm Res*., 17, 475-481 (2018) DOI: 10.4314/tjpr.v17i3.13

115. X Li, Y Song, P Zhang, H Zhu, L Chen, Y Xiao, Y Xing: Oleanolic acid inhibits cell survival and proliferation of prostate cancer cells *in vitro* and *in vivo* through the PI3K/Akt pathway. *Tumor Biol*., 37, 7599-7613 (2015) DOI: 10.1007/s13277-015-4655-9

116. J Liu: Pharmacology of oleanolic acid and ursolic acid. *J Ethnopharmacol*., 49, 57-68 (1995) DOI: 10.1016/0378-8741(95)90032-2

117. T B Ayeleso, M G Matumba, E Mukwevho: Oleanolic acid and its derivatives: biological activities and therapeutic potential in chronic diseases. *Molecules*, 22, 1-16 (2017) DOI: 10.3390/molecules22111915

118. R E De Angel, S M Smith, R D Glickman, S N Perkins, S D Hursting: Antitumor effects of ursolic acid in a mouse model of postmenopausal breast cancer. *Nutr. Cancer*., 62, 1074-1086 (2013) DOI: 10.1080/01635581.2010.492092

119. L S Baumann, Ursolic acid. (cited 03-10-2018); Available from: https://www.mdedge.com/edermatologynews/article/133487/aesthetic-dermatology/ursolic-acid.

120. M K Ediriweera, P Jayarathna, K H Tennekoon, S R Samarakoon, I Thabrew, E H Karunanayake, A Adhikari: Campnospermenone A, B and C, three new cytotoxic alkyl-hydroxycyclohexenones from *Campnosperma zeylanica* Thwaites leaves. *Phytochem Lett*., 24, 114-119 (2018) DOI: 10.1016/j.phytol.2018.01.018

121. D J Newman, G M Cragg, K M Snader: Natural products as sources of new drugs over the period 1981-2002. *J. Nat. Prod.*, 66, 1022-1037 (2003) DOI: 10.1021/np030096l

122. B Patwardhan, R A Mashelkar: Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? *Drug Discov. Today*., 14, 804-811 (2009) DOI: 10.1016/j.drudis.2009.05.009

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