Review Article

Plant-based natural compounds and herbal extracts as promising apoptotic agents: their implications for cancer prevention and treatment.

Aadil Khursheed 1, Manzoor A. Rather *2, Rafiya Rashid 3

1 Department of Physical Sciences, Lovely Professional University, Punjab-India.
2 Department of Chemistry, Sheikh-Ul Alam Memorial Degree College Budgam, Srinagar-India.
3 Department of Botany, Sheikh-Ul Alam Memorial Degree College Budgam, Srinagar-India.

*Corresponding Author: Manzoor A. Rather
Department of Chemistry, Sheikh-Ul Alam Memorial Degree College Budgam, Srinagar-India.
E-mail address: manzooriiim@ymail.com

Running Title: Plant-based natural compounds as apoptotic agents

Received: 29 April, 2016; Revised: 17 May, 2016 Accepted: 13 June, 2016

Available online at http://www.thescientificpub.com http://dx.doi.org/10.19046/abp.v03i03.08

Abstract

Natural products continue to impress drug discovery scientists by their amazing bioactivity profiles coupled with their highly complex molecular architecture. These compounds have been the principal source of anticancer chemotherapeutic agents over the last few decades. About 60-70% of the anticancer drugs which are clinically used have been either pure natural products, their synthetic or semi-synthetic derivatives. Among natural products, plant-derived compounds play a pivotal role in anticancer drug discovery programme. These plant-derived compounds include vincristine, vinblastine, camptothecin and its derivatives, etoposide, topotecan, irinotecan, paclitaxel etc. Various novel and promising anticancer drugs are currently under various phases of clinical trials. Natural products have seen many ups and downs viz-a-viz their role in cancer chemotherapy. During 90's these compounds saw a dip in the top-notch pharmaceutical companies mainly because of the high throughput screening programmes which involve targeted therapies using small molecules. However, barring few cancers, these therapies were confronted with the ineffectiveness with respect to several solid tumors. This has hugely revitalized their importance in anticancer drug discovery. The current review focuses on the plant-based natural compounds and herbal extracts which specifically induce anticancer effects via the induction of apoptosis. This review also discusses their mode of action along with their botanical origin.

Keywords: Natural products, apoptosis, anticancer drugs, chemotherapy, vinblastine, paclitaxel.

Introduction

Apoptosis is a form of cell death in which a programmed order of actions results in the elimination of cells without releasing the toxic substances into nearby areas [1]. Apoptosis plays an essential role among multi-cellular organisms whereby it maintains the health of the body by eliminating the old cells, excessive cells and unhealthy cells. The biochemical order of events causes different changes in cell morphology which ultimately results in cell death. The series of sequential events include cell shrinkage, chromatin condensation, blebbing, nuclear fragmentation, chromosomal DNA fragmentation, and global mRNA decay. In an average human adult 50-70 billion cells due to apoptosis die each day [2] while as in an average child having age in between 8-14 approximately 20-30 billion cells die each day due to this phenomenon [3]. In comparison with necrosis which is a way of traumatic cell death caused by an acute cell injury, this process is highly controlled and highly regulated which makes it advantageous in organisms life cycle. In a
developing human embryo separation between fingers and toes is a result of apoptosis. Apoptotic cell bodies are produced by apoptosis which are engulfed easily by the phagocytes and quickly removed before the cell releases its toxic substances and causes damage to the nearby cells [4]. Once apoptosis has started it cannot stop on its own as it is a highly regulated process. There are two different pathways by which apoptosis can be initiated: intrinsic and extrinsic pathways. In the intrinsic pathway cell kills itself when it senses stress from the nearby cells while as in the extrinsic pathway the cell kills itself when it receives a signal from other cells or from the body. Either of the causes cell death by initiating caspases, caspases are the enzymes that degrades proteins also known as proteases. At first in both of the pathways the process is initiated by initiator caspases, after that to degrade proteins haphazardly executioner caspases are activated to kill the cell.

Until 1965, apoptosis was not given much interest till John Foxton Ross Kerr at University of Queensland was able to differentiate between traumatic cell death and apoptosis while he was studying tissues by electron microscopy [5]. Apoptosis can always be detected in untreated malignant neoplasms and it participates in the regression that follows at least some forms of therapy. It is also found in many of the tissues of healthy animals and its focal appearance at specific times during normal ontogenesis indicates that it is implicated in the fashioning of developing organs and digits, and in the involution of phylogenetic vestiges in the embryo [6]. In adrenocorticotrophic hormone (ACTH) withdrawal from adrenal gland apoptosis is more prominent, apoptosis is also involved in different types of atrophy also [7]. When apoptotic bodies are found in the histological sections of tissue it means that an extensive cell drop out or cell elimination is taking place in the tissue. Manifestation of apoptosis in healthy animals is interesting though it is hardly understood in presence of tangible bodies in the germinal centres of lymphoid follicles that are represented by the examination of electron micrographs and histological features of apoptotic bodies [8]. It indicates to us that following phagocytosis they undergo the classic sequence of changes. Many of them have been shown to be derived from cells that have recently synthesized DNA [9] and cell death in lymphoid follicles might be an inevitable consequence of rapid cell proliferation.

**Role of apoptosis in different human diseases**

Numerous diseases can be caused by uncontrolled cell death or excessive apoptosis such as hematologic diseases, neurodegenerative diseases and general tissue damage. So far as HIV is considered, its succession is directly related to the extensive apoptosis. In a normal human being the number of CD4+ lymphocytes is in equilibrium with the cells which are continuously produced in bone marrow. However, there is an inability of bone marrow in the HIV patients to regenerate these CD4+ lymphocytes and hence the loss of this balance. CD4+ lymphocytes die at a very fast rate when stimulation of apoptosis is done by HIV. The progression of the human immunodeficiency virus infection into AIDS due to the depletion of CD4+ T-helper lymphocytes in fact is the result of this uncontrolled cell death due to inability of the bone marrow to main equilibrium. This resulted in the negotiable immune system and makes a typical sense of symptoms for AIDS (loss of immune system). Direct consequence of viral infection may also result in cell death. HIV-1 manifestation results in tubular cell G2/M arrest and apoptosis [11]. In the same manner ascoviruses cause viral infection and also replication by the induction of apoptosis. Additionally, cell fragmentation also takes place upon the viral establishment of the apoptosis and in order to form the vesicles it is postulated that virus utilizes apoptosis [12]. Viruses can remain intact from apoptosis particularly in the latter stages of infection. Ascoviruses can be exported in apoptotic bodies that pinch off through the normal apoptotic procedure from the surface of the dying cell. Viral phages in these apoptotic bodies are then consumed by phagocytes, which prevent the initiation of a host immune response. Amusingly, it was found that viruses not only induce diseases on the basis of enhancing apoptosis but also by suppressing it. An important aspect of multicellular organisms is their ability to fight extensive body infection through apoptosis. There are certain viruses that can halt this process and result in their own invasion into the cell. Viral infection causes apoptosis ordinarily, either by the host’s immune response or directly. The main reason behind cell death is that body wants to reduce production of new virus and further infection. Unfortunately, new suppressive mechanisms have been evolved in many viruses that spoil the defensive mechanism of cell destruction. Viruses involves a large variety of mechanisms to suppress the apoptosis like; activation of the protein kinase R (PKR), expression of viral proteins coupled to the major histocompatibility complex (MHC) proteins on the surface of the infected cell [13]. There are more than eighty thousand publications over apoptosis but still exact reason of cell death is still debated. In the nematode, caenorhabditis cell death is not caused by apoptosis.
Figure 1: Schematic diagram of apoptotic events: The series of sequential events include cell shrinkage, chromatin condensation, blebbing, nuclear fragmentation, chromosomal DNA fragmentation in apoptosis.
Role of apoptosis in cancer

Inhibition or suppression of apoptosis results in different cancers, inflammatory diseases, viral infections and autoimmune diseases. It was believed earlier that the increase in cellular proliferation is only associated with increase in accumulation of cells, but now it is also known that decrease in cell death is also responsible for cell proliferation. Most common disease among the above given diseases is cancer. It is a result of excessive cellular proliferation, which may be also described as over expression of IAP family members which causes the abnormal response of malignant cells to apoptosis induction: cell cycle-regulating genes (such as p53, ras or c-myc) are inactivated or mutated in contaminated cells, and further genes (such as Bcl-2) also modify their expression in tumors.

Why we need apoptotic inducers in cancer chemotherapy

The present accepted models for the treatment of cancer involves drugs, surgery, radiation or all of them in combination. Sometimes chemotherapeutic agents results in the relief from the symptoms, increase in life and occasionally cures the disease. An ideal drug for the treatment of cancer is the one which causes less harm to the normal cells. Modulation of apoptosis may be helpful in the therapy and management or avoiding cancer. Synthesis of the better drugs however remains an important aspect in research. Large work has been done on synthesis but only a small number of prototypes have evolved. There is an immediate and continuous need for prototypes and the use of new templates which can serve as strong chemotherapeutic agents. More importantly natural products are providing the same and they fit in such models. Epidemiological studies have shown that the risk of the developing cancer due to the consumption of the fresh fruits and vegetables, major sources of micronutrients and phytochemicals may be reduced [14].

Certain known products from plants induce apoptosis in neoplastic cells but not in normal cells [15]. Increasingly it has become apparent that apoptosis for many anti-tumor agents is an important mode of action, including alkylating agents such as cisplatin and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU)[16], ionizing radiation [17], topoisomerase inhibitor etopside [18], cytokine tumour necrosis factor (TNF) [19], taxol [20], and N-substituted benzamides like 3-chloroprocainamide and metoclopramide [21]. For innovative mechanism-based drug discovery apoptotic induction has been a new target [22]. It is considered more valuable to monitor extracts of plants either in crude form or isolated form which are apoptosis inducers. It has been evolved from various studies that plant extracts are more useful in prevention of cancer. Chemopreventive agents includes a vast group of compounds with variety of mechanisms of action, but, their crucial ability to persuade apoptosis may show a merging concept for the mechanism of chemoprevention. The useful information may be deduced by understanding the modes of action of these compounds regarding cancer avoidance and cancer therapy.

Plant extracts as promising apoptotic inducers in traditional medicine

Solanum muricatum (Pepino) extracts caused the apoptotic death in liver (QSY-7721, SKHEP-1), prostate (PC-3, DUI-45), stomach (MKN-45), breast (MDA-MB-435), lung (NCI-H-209) ovarian (OVCAR) and colon (HT-29) cancer cells and also in some of the normal cells present in the culture like NHP, HUVEC, WI-38 etc. Pepino extract is also found to be responsible for the formation of ladder due to DNA and PARP cleavage [23]. Zingiberaceae (Alpinia oxyphylla Miquel) is traditionally oriented herbal medicine which results in the induction of apoptosis driven cytotoxicity to HL-60 cells in the culture [24]. Observations unpublished from the authors’ laboratory have exposed that Tiliacora racemosa Colebr. ethanolic extracts from roots and leaves, and Semecarpus anacardium Linn. nuts in the Ayurvedic oil preparation have cytotoxic potential towards cell lines K-562 and HL-60. It should be noted that these plants which are used in traditional Indian medicine bring cell death through apoptosis. Viscum album L. (Loranthaceae). European mistletoe, extract is one of the most broadly used substitute cancer therapies in Europe and has been predicted to cause cytotoxicity to human lymphocytes, probably through apoptosis[25,26]. Preparations of Mistletoe from the host trees Malus, Pinus, Quercus, and Abies when clinically used resulted in the induction of apoptosis [27] PC-SPES a Chinese herbal supplement has shown to induce apoptosis in MUTU- 1 cells dose-dependent downregulation of bcl-6 [28]. Salvia miltiorrhiza is a traditionally used more common Chinese herbal medicine to cure liver diseases in China for decades. This plant extract from salvia miltiorrhiza resulted in clear cytotoxic effects and potentially subdued the proliferation of human hepatoma cell line, HepG-2 through apoptosis [29].

Artemisia capillaris Thunberg water-soluble macromolecular components revealed suppression of apoptosis and cell proliferation when it was considered on human hepatoma cell line (SMMC-7721) [30]. Conifer Tetraclinis articulata essential oil showed its cytotoxic effect on a variety of human cancer cell lines and...
peripheral blood lymphocytes which is driven through apoptosis [31]. Induction of apoptosis in Chinese hamster ovary (CHO) cells is a result of the aqueous extract of this plant [32]. To treat breast tumours and inflammation seeds from Acalypha wilkesiana (Euphorbiaceae), are essential components of a complex plant mixture used empirically by traditional healers in south-west Nigeria. [33]. Bussing et al. [33] observed generation of reactive oxygen intermediates and an induction of apoptosis in granulocytes by an aqueous extract of these seeds. Release of pro-inflammatory cytokines TNF-α and interleukin-6 (IL-6) and also T-cell associated cytokines interleukin-5 (IL-5) and interferon-gamma (IFN-γ) is induced by the use of this extract.

Natural products

Natural product is a chemical compound or substance which is being either naturally produced or produced by a living organism [34]. Any substance produced by different forms of life including plants and microbes in a broader sense belongs to natural products [35]. Natural products can be prepared by chemical synthesis including both semisynthesis and total synthesis. They play an important role in developing the organic chemistry by opening new and challenging synthetic targets. Cosmetics, dietary supplements and foods produced from natural sources without added artificial ingredients are an extension of natural products. Within the scope of organic chemistry natural products are defined as purified organic compounds that are produced by the primary or the secondary metabolism in the natural sources [36]. In medicinal chemistry the definition of natural products is confined to only secondary metabolites [37, 38]. Evolutionary advantage is provided by the secondary metabolites otherwise they are not essential for survival [39].

Flavonoids

Common components present in human diet are a family of polyphenolic compounds that are flavonoids in nature. They occur naturally in a broad range of fruits and vegetables and are widely distributed in the plant kingdom [40]. Currently, polyphenolic phytochemicals are of intense interest, including flavonoids, this is because epidemiological data and experimental data support the view that some of flavonoids exert beneficial effects, including cardioprotective, anti-inflammatory, antioxidant, and anti-carcinogenic activities [41,42]. The antioxidant properties of flavonoids that are present in foods are being mostly focused upon and exploited [43]. The bioavailability of these dietary compounds is commonly too low to have any substantial direct effect on reactive radical species, although antioxidant properties are important. Besides having free-radical scavenging activity, recent work has shown that, flavonoids can also affect a variety of signalling enzymes, including cellular proteins [44,45] and transcription factors [46,47]. Flavonoids may exert a wide range of biological effects, recent data has indicated that these molecules can control apoptotic cell death [48,49]. For the development and homeostasis of multi-cellular organisms apoptosis is a highly conserved and well-controlled process of cell death that is required. A variety of extrinsic signals results in triggering of apoptosis by radiation, growth factor withdrawal, Fas, and tumor necrosis factor (TNF)-α ligands and also intrinsic stimuli p53, oxidative stress; [50,51]. Nevertheless, pathological processes, including cancer, autoimmunity, and neurodegenerative disorders are associated with disorders in this physiological cell death program [52]. Some malignant cells have a reduced ability to die by apoptosis in response to physiological stimuli was indicated by a great deal of evidence[53]. Hence, it is highly desirable to extend chemicals that can trigger or sensitize resistant cells to apoptosis. In addition to this the use of natural compounds as chemopreventive or cytotoxic agents might be a promising strategy in cancer prevention and therapy. Genistein (a hydroxyisoflavone) induced apoptosis in human pro-myelocytic HL-60 leukaemic cells it was suggested by flow cytometric analysis [54]. Genistein is also accounted to suppress angiogenesis [55], tyrosine kinase [56] and cell-cycle progression [57].

It was reported that pure soy isoflavones like genistin, genistein, daidzein and biochanin A (figure 3) and soy phytochemical contemplate shows dose-dependent growth inhibition of murine MB-49 and MBT-2 and human HT-1376, UM-UC-3, RT-4, J-82 and TCCSUP bladder cancer cell lines and also causes cell death by the phenomenon of apoptosis [58].
Figure 2: Some of the naturally occurring bioactive compounds.
Plant-based natural compounds as apoptotic agents

Advances in Biomedicine and Pharmacy Vol. 3 (3) 2016

Figure 3: Genistin, genistein, daidzein and biochanin A are some of the key flavonoids which show the potential against different cancers.

Alkaloids

Figure 4: Opium poppy (*Papaver somniferum*) from which morphine, the first alkaloid was isolated.
Naturally occurring chemical compounds that contain mostly basic nitrogen atoms are known as Alkaloids. Neutral [59] and even weakly acidic properties [60] related compounds are also included in this group. Similar structural synthetic compounds are also termed as alkaloids [61]. Alkaloids may also contain oxygen, sulfur and, more rarely, other elements such as chlorine, bromine, and phosphorus in addition to carbon, hydrogen and nitrogen. Morphine, is first individual alkaloid which was isolated in 1804 from the opium poppy (Papaver somniferum). Chinese herb, Solanum incanum, contains Solamargine, an alkaloid purified has been observed to provoke apoptosis in Hep-3B (human hepatocyte) and normal skin fibroblast cells in culture [62]. TNF receptor I was up-regulated within 30 min of solamargine treatment in addition to the gene expression. TNF receptor I over-expression may be related to the mechanism of cytotoxicity of solamargine because it has been involved in apoptosis[62]. Stephania sutchuenensis, is the species from which sinococuline is isolated and it has been found effective in inducing inhibition of cell-growth in mouse fibroblast cell line (L-929), a rat alveolar macrophage culture and HL-60 in a dose-dependent manner. In vitro exposure of sinococuline also malformed the macrophage function by dropping the production of TNF and reactive nitrogen intermediates. Sinococuline seems to activate the mode of death induced by apoptosis [63]. Microphilis guyanensis and Genipa americana collected from the rainforest of Suriname. Bioassay guided fractionation of an extract yielded the known alkaloid cryptolepine as the major active compound. Numerous cryptolepine derivatives were manufactured. The parent compound in the yeast assay system has the higher potency than the structurally modified compounds, even if some cryptolepine derivatives did show significant cytotoxicity in mammalian cell culture, through the molecular mechanism of apoptosis[64]. Several bis-benzylisoquinoline alkaloids which were isolated from Tiliacora racemosa root induced apoptosis in K-562 cells (Taraphdar et al., unpublished observations). The Chinese tree, Camptotheca acuminata Decsne, Nyssaceae, contains an alkaloid Camptothecin (CPT), isolated from the stem wood, is a topoisomerase I inhibitor and results in apoptosis in a human leukaemia cell line PLB-985 cells. After neutrophilic differentiation sensitivity to CPT was enhanced, but after monocyte differentiation was lost. Catalase partially inhibited CPT and pyrroline dithiocarbamate (an antioxidant inhibitor of NF-kB) caused DNA fragmentation to happen in granulocytic differentiated PLB-985 cells. Reactive oxygen intermediates were generated in CPT-treated PLB-985 cells it was revealed by flow cytometry analysis and suggested that oxygen radicals generated by NADPH oxidase might contribute directly or indirectly to apoptosis which is induced by CPT in human leukaemia and in neutrophilic differentiated cells [65]. 7-hydroxystaurosporine (UCN-01), a natural alkaloid was reported to increase cis-diammine-dichloroplatinum (II) cytotoxicity and apoptosis in ovarian cancer cells [66].

**Terpenoids**

D-limonene and perillyl alcohol (POH) are monoterpenes and are derived from orange peels and lavender, respectively. They have been exposed to possess chemopreventive properties against liver, mammmary and lung carcinogenesis. It has been reported by Reddy et al. that the colon tumours of animals as compared to those fed with control diet, those which were fed with POH demonstrated increased apoptosis. In advanced rat mammary carcinomas chemotherapy with POH in another experiment revealed that apoptosis was induced within 48 h [67]. Ultra-structural and Gross morphology of POH governed tumour regression indicated that there was reduction of apoptosis accounted in the epithelial component. The most plentiful monocyclicmonoterpene D-limonene in orange peel oil resulted in inhibition of development of gastric cancer through decreased DNA synthesis and increased apoptosis [68].

Limonene attenuates enhanced gastric carcinogenesis by sodium chloride via decreased ornithine decarboxylase activity and increased apoptosis [69]. From hop extract Humulone, a bone resorption inhibitor was isolated which induced apoptosis in the leukaemia cell line HL-60 at low doses [70]. Diterpene taxol (figure 2) from Taxus brevifolia Nutt. (Tanaceae) exerts the cytotoxic effect that represents both inhibition of cell death and cell proliferation. The drug also induced apoptosis and blocked cells in the G2/M phase of the cell cycle. Taxol stabilized the spindle during mitosis and this mitotic block led to the inhibition of apoptosis and cell proliferation in lower concentration range. Microtubule polymerization and increased stimulation of the formation of microtubule bundles which blocked entry into S phase and led to the inhibition of cell proliferation and induction of necrosis in higher concentration range of taxol [71]. Independent of microtubules and G2/M arrest, cell death induced by paclitaxel, on the other hand occurs via a signalling pathway [72]. Some of the examples of terpenoids are given below (figure 6).
Figure 5: Some of the naturally occurring bioactive alkaloids which exhibit the potential to be used as apoptotic inducers.

Figure 6: Some of the representative terpenoid compounds which show anticancer potential against different cancer cells.
Polyphenols

It is believed that human individuals may consume as much as one gram of plant phenols per day in their diet and the human diet contains a complex mixture of plant polyphenols [73, 74]. These phenols have shown that cytotoxic effect against different tumours is mediated through apoptosis. Studies have revealed [75] that various transformed cell lines such as HL-60 RG human promyelocytic leukaemia, P-388 D1 mouse lymphoid neoplasms, HeLa human epithelial carcinoma, PLC/PRF/5 human hepatoma, dRLh-84 rat hepatoma and KB human epidermoid carcinoma gallic acid selectively induces cell death [75]. This plant phenol which induced DNA fragmentation, is a well-known natural antioxidant, in four different human myelogenous leukaemic cell lines HL-60, 6L-1, U-937 and THP-1, but it is not helpful over human erythroleukaemic K- 562 and T-cell leukaemia MOLT-4 cell lines. In contrast, caffeic acid and tannic acid induced DNA fragmentation only in HL-60 cells [76]. Whereas two other phenylpropanoid monomers, i.e. p-coumaric acid and ferulic acid were inactive, caffeic acid induced DNA fragmentation. Caffeic acid has a dehydrogenation polymer which showed a little lower activity than its consequent monomer, but dehydrogenation polymers of p-ferulic acid and coumaric acid were inactive [76]. Caffeic acid phenethyl ester (CAPE), the folk medicine propolis, is the active component which displayed selective cytotoxicity toward oncogene-transformed CREF (cloned rat embryo fibroblast) cells through apoptosis [87]. The bcl-2 had a protective effect against CAPE-induced cell death. The major pigment in turmeric is Curcumin, a phenolic compound that has been identified, induces apoptosis in transformed human cells and rodent in culture [78, 79]. Since, it has no apparent effect on non-tumourigenic rat embryo fibroblast cells, which makes it a helpful accessory to chemotherapy. Through inhibition of cyclooxygenase (COX) metabolites curcumin mediated the chemopreventive action, a mechanism can be provided by it for induction of apoptosis [80, 81]. 1-[4¢-hydroxy-3¢-methoxyphenyl]-7-phenyl-3-heptanone (Yakuchinone A) and (1-[4¢-hydroxy-3¢-methoxyphenyl]-7-phenylhept-1-en-3-one) (yakuchinone B), these are obtained from A. Oxyphylla, and are reported to have apoptotic inducer activity in HL-60 cells due to the presence of a diarylheptanoid moiety with a carbonyl functional group [82]. Arachidonic acid metabolism is inhibited by these phenolics that has been associated to stimulation of programmed death in definite types of tumour cells [83, 84]. To activate transcription factor activator protein-1 (AP-1) in immortalized mouse fibroblast cells in culture which may be due to pro-oxidant activity of these compounds. Chilli pepper (C. Frutescens L.) and hot red pepper (Capsicum annum L.) contains the phenolic substance named capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) the principal pungent ingredient present and this substance has been found to induce apoptosis in HL-60 cells in culture [85]. Caffeic acid, ferulic acid and p-coumaric acid structures are shown in figure 7.

Xanthones

Xanthones are simple three-membered heterocyclic ring compounds mainly found as secondary metabolites in higher plants and microorganisms. Depending on their diverse structures modified by substituents on the ring system, xanthones have diverse biological properties including antioxidative, antihypertensive, antithrombotic and anticancer [86]. Xanthone derivatives have attracted many scientists to isolate or synthesize xanthone compounds as novel drug candidates because of their notable structural scaffold and pharmacological importance. The two major sources of xanthone derivatives are; either they are synthesized or isolated from natural resources (plant or marine materials). [87]. Although Xanthone based compounds hold several reviews [88, 89] and some of them have focused towards one of the most important area of cancer therapy. We are going to provide you a summary of xanthone’s that have recently found to be prospective and novel anticancer drug candidates. Some biological targets of xanthones [90] are apoptosis, DNA intercalation, DNA alkylation etc. Most of the xanthones are recognized from natural resources of plant origin. Cancer-preventive xanthone derivatives have been isolated from marine fungus species recently. The metabolic activation and excretion process of xenobiotics, chemopreventive agents are known to act on the enzymes related to these processes. Xenobiotics are transformed to more hydrophilic species for detoxification.
by the enzymes specifically involved in phase I metabolism transform, but some of these enzymes result in an increase in the risk of producing carcinogens, which can lead to carcinogenesis by interacting with DNA.

Figure 8: Some of the structures from xanthones which may act as promising anticancer agents.

[91] Marine organisms or algae might be a good source of chemopreventive xanthone derivatives. A xanthone, α-mangostin, separated from the pericarps of mangosteen, Garcinia mangostana, inhibited cell growth of a human leukaemia cell line by inducing caspase-3 dependent apoptosis [92,93]. Further studies revealed that [94], these compounds are used as potent anticancer agents (figure 8).

Coumarins

The class name Coumarins have been derived from ‘Coumarou’; it is the vernacular name of the tonka bean (Dipteryx odorata Willd., Fabaceae), from which isolation of coumarin itself was done in 1820 [95]. Coumarin belongs to one of benzopyrone family of compounds, all of which consist of a benzene ring joined to a pyrone ring [96]. The benzo-α-pyrone and the benzo-g-pyrone of which the coumarins belong are the two subdivisions of benzopyrones of which the flavonoids are principal members. Figure 9: Represents two forms of benzopyrone [A] & [B].

Since 1954, FDA has classified coumarin as toxic substance, following reports that it causes possible liver tumour-producing properties in rats [97], all foods containing coumarin were banned by the FDA and labelled it as an adulterant [98]. Chemical carcinogenic nature of coumarin was referred due to tests performed on rodents and thus it was labelled as carcinogenic by National Institute for Occupational Safety and Health (NIOSH). However, in extrapolating this information to human situations caution needs to be taken. Coumarin and its metabolites are non-mutagenic as it was deduced by performing various tests (Ames, micronucleus) [99], [100]. Numerous studies have shown the acute, chronic and carcinogenic effects of coumarins using rat and mouse models. Hepatic biochemical and morphological changes have been examined for various periods of coumarin administration in studies involving the rat (1 week to 2 years). Liver necrosis and increased plasma transaminase activities in DBA/2 strain mice were a result of single oral dose of coumarin [101]. There are numerous coumarins obtained from microbes. Some important coumarins obtained from microbial sources are; Novobiocin, Coumermycin A1 and Clorobiocin.

(Figure 10)
Table 1: The table representing four main Coumarin subtypes with main structural features and examples of each coumarin subtype.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Features</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple coumarins</td>
<td>Hydroxylated, alkoxylated or</td>
<td><img src="image" alt="7-hydroxycoumarin" /></td>
</tr>
<tr>
<td></td>
<td>alkylated on benzene ring.</td>
<td></td>
</tr>
<tr>
<td>Furanocoumarins</td>
<td>5-membered furan ring attached to</td>
<td><img src="image" alt="7-hydroxycoumarin" /></td>
</tr>
<tr>
<td></td>
<td>benzene ring linear or angular.</td>
<td><img src="image" alt="angelicin" /></td>
</tr>
<tr>
<td>Pyranocoumarins</td>
<td>6-membered pyran ring attached to</td>
<td><img src="image" alt="Seselin" /></td>
</tr>
<tr>
<td></td>
<td>benzene ring linear or angular</td>
<td><img src="image" alt="xanthyletin" /></td>
</tr>
<tr>
<td>Pyrone-substituted</td>
<td>Substitution on pyrone ring, often</td>
<td><img src="image" alt="warfarin" /></td>
</tr>
<tr>
<td>coumarins</td>
<td>at 3-C or 4-C positions</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Represents the structure of group A saponins consider (C) above as the basic structure.

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soyasaponin Aa</td>
<td>CH₂OH</td>
<td>β-D-Glc</td>
</tr>
<tr>
<td>Soyasaponin Ab</td>
<td>CH₂OH</td>
<td>β-D-Glc</td>
</tr>
<tr>
<td>Soyasaponin Ac</td>
<td>CH₂OH</td>
<td>α-L-Rha</td>
</tr>
<tr>
<td>Soyasaponin Ad</td>
<td>H</td>
<td>β-D-Glc</td>
</tr>
<tr>
<td>Soyasaponin Ae</td>
<td>CH₂OH</td>
<td>H</td>
</tr>
<tr>
<td>Soyasaponin Af</td>
<td>CH₂OH</td>
<td>H</td>
</tr>
<tr>
<td>Soyasaponin Ag</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Soyasaponin Ah</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
Figure 10: Some of the group A saponins which exhibit anticancer potential.
Figure 11: Some of the group A saponins which exhibit anticancer potential.
Saponins

In China, Korea and Japan, Ginseng has been used for thousands of years, predominantly for its broad spectrum medicinal effects such as immunomodulatory, tonic, adaptogenic, and anti-aging activities (1Ð3). The best known Asian species is Panax ginseng whereas the American species belongs to Panax quinquefolius and these two ginseng species are available as medicinal herbs. Both species are broadly used in Asian countries for a diversity of purposes. It was accounted that daily utilization of ginseng extract inhibited prostate weight and amplified the serum testosterone level in male rats [102], after exposing LNCaP cells to ginseng extract, no significant expression of PSA was detected [103], and to anti-androgenic activity its activity may not be attributed [104]. Chemical analysis of ginseng has shown the existence of many ingredients, including sugars, organic acids, inorganic salts, vitamins, sterols, oligopeptides, volatile oils, polysaccharides, and saponins. Saponins are commonly known as ginsenosides. They are well considered for their biological properties. The ginseng saponins can be divided into three groups in general, taking in account the structure of the non-sugar glycon part of the molecule: (a) 20(S)-protopanaxadiol type, such as ginsenosides Ra, Rb, Rc, Rd, Rg3, Rh2 and Rs; (b) oleanolic acid type, such as ginsenoside R0; and (c) 20(S)-protopanaxatriol type, such as ginsenosides Re, Rf, Rg1, Rg2 and Rh1. Till date, a total of over 60 ginsenosides were isolated from members of the Panax genus, more than 30 ginsenosides have been found in the roots and other parts of P. ginseng [105]. Medicinal effects such as induction of cancer cell differentiation [106] and angiogenesis is a result of these compounds, On the other hand, cautions have been raised in order to safeguard consumers using these herbal medicines (10Ð11). American ginseng inhibited the human prostate cancer as demonstrated by using LNCaP cells. [107]. Through a mitochondrial-mediated pathway Saponins isolated from Asparagus induce apoptosis in human hepatoma cell line HepG2 [108].

Anthocyanins

The basic structure of anthocyanins is given in figure 13. They are vacular water-soluble pigments that may appear purple, red, or blue depending at different pH values (figure 14). Flavonoids are a parent class of molecules they belong to. They are synthesized via the phenylpropanoid pathway. Anthocyanins basically are odorless and nearly flavourless, contributing to taste as a moderately astringent sensation. All tissues of higher plants contains Anthocyanins, including roots, leaves, flowers, stems, and fruits. Anthoxanthins are clear, white to yellow counterparts of anthocyanins occurring in plants. Anthocyanidins act as precursors for Anthocyanins, anthocyanins are formed by adding sugars to anthocyanidins [109]. In many berries, dark grapes, cabbages and other pigmented foods, plants, and vegetables anthocyanins are the largest group of pigments present. They possess antioxidant activities, which possibly will help in the explanation of their anti-atherosclerotic [112], anti-carcinogenic [113], and anti-inflammatory [114] properties. The main anthocyanin present in juice of pigmented oranges is cyanidin-3-O-b-glucopyranoside (Cy-g) (figure 15), it is most effective antioxidant as per reports.[115,116]. Because of its peculiar redox potential it acts as a real antioxidant and not as a simple metal-chelating compound [117]. Resveratrol and ascorbic acid has lower antioxidant activity than this compound, even if, they are considered as most active natural antioxidants.
Figure 14: Varying colours of anthocyanins with varying pH.

Figure 15: Cyanidin-3-O-b-glucopyranoside
Role of natural products in cancer chemotherapy

Natural products have always played a major role in the health sector since time immemorial. The use of microbial secondary metabolites and plants has supported in doubling of our life span in the 20th century. They have reduced suffering and pain, and reformed medicine by allowing the transplantation of organs. Since their chemical multiplicity is based on geographical and biological diversity, researchers have explored the entire globe for bioprospecting. Aquatic environment especially oceanic life hosts a vast range of life forms crammed with natural products of probable pharmaceutical significance. Marine bioprospecting is a comparatively novel experience; thus, marine life is a comparatively uncharted area of opportunity. New processes are being formulated to produce the so-called ‘unculturable’ microbes from both the sea and the soil. Secondary metabolites with complex structures are most biologically active natural products. Sometimes the natural product itself can be used, but not always, derivatives made biologically or chemically are the molecules used in medicine. Biosynthetic pathways are frequently genetically influenced to form the required product. Thousands of new derivatives can now be made by this biological technique with the dawn of combinatorial biosynthesis, which is corresponding to combinatorial chemistry.

Needs and challenges of the natural environment resulted in the evolution of secondary metabolism and is being frequently carried out on its own [120] for time period of over three billion years in which inhabitation of bacteria on the earth have taken place [121]. There has been an evolutionary process going on in that time period in which producers of secondary metabolites developed with respect to their confined environments. Genetic modifications and the biosynthetic genes were reserved further improving the process, if the metabolites were useful to the producing species. [120]. Nature has resulted in a number of products and amazing variety. Using high-throughput screening and fermentation this natural wealth is tapped over using plant option to this process. Reduced weight less structural environment resulted to generate new secondary metabolites related to this process, if the metabolism were reserved further improving the process, if the metabolites were useful to the producing species. The induction of apoptosis in malignant tissues or cancer products, and altered with complex red over using plant option to this process. A number of natural products produced by plants has been approximated to be between 500 000 and 600 000 [122, 123]. By the late 1990s, Structures of about 160 000 natural products were already elucidated a value mounting by 10 000 per year [124]. About 100 000 out of the above number of natural products are isolated from plants. Microbial secondary metabolites are also present there and are more than 20 000 in number [125]. There are about 200 000 to 250 000 biologically active products, with regard to biological activity (active and/or toxic). About 100 000 secondary metabolites of Molecular weight less than 2500 have been characterized. Half are produced by microbes and other half by plants [126, 127].

Clinical trials

In clinical trials many of the terrestrial natural products succeeded and have effectively served in medicine for over 50 years. Over 60% of pre-NDAs and approved candidates are either natural products or related to them, it does not include biologicals such as monoclonal antibodies and vaccines [128]. 5% are synthetic with natural product pharmacophores, 27% percent are natural products, and 23% are synthetic mimics of natural products. Approximately half of the best-selling pharmaceuticals are natural or they are related to natural products. There were 225 natural product-based drugs in various testing procedures such as clinical phases I to III, preclinical, and preregistration in early 2008 [129]. Out of these 7 were fungal in origin, 24 from animals, 25 were from bacteria, 61 were semisynthetic, and 108 were from plants. 22 of marine natural products or their chemical derivatives are in clinical trials, out of 18 000.

Conclusion

Elimination of damaged and abnormal cells takes place physiologically through a highly organised programmed cell death; Apoptosis. It is an important process going on in multicellular organisms, any disruption to this process leads to serious impacts like abnormal growth-cancer. Apoptotic cells show a very much specific chemical features and also definite characteristic morphology. An efficient approach recognized for cancer chemotherapy is the induction of apoptosis in malignant tissues or cancer cells. Apoptosis also lets us to analyze markers for the estimation of potential agents for cancer prevention. A huge number of natural products results in chemoprevention and cytotoxic activity. The mode of action for many of these compounds goes via apoptosis. Traditionally used medicines where totally based on plant extracts and maximum of them have a similar mode of action. Natural products have vast applications and hence many more screening studies are required over using plant

General overview of natural compounds

Near about a million natural products are known. The number of natural products produced by plants has been
extracts and isolated compounds from them. The apoptotic agents should only be cytotoxic to the damaged and abnormal cells, it should not affect the immune system and normal body cells. Naturally occurring compounds that are included in the diet are non-toxic and may partially regulate programmed cell death in several tissues and organs. The number of naturally occurring compounds discussed above such as Flavonoids, alkaloids, polyphenols, terpenoids, xanthenes, coumarins, anthocyanins and saponins all belongs to a family of natural products and various compounds belonging to the classes show potential to induce apoptosis. There are numerous natural products which are being isolated and are served as medicine in the market. They have least side effects due to their natural occurrence. Some of them are still in the chemical trials. Hence plant based natural products and herbal extracts are promising apoptotic agents and they play a crucial role in cancer prevention and treatment.

Acknowledgement
None declared

Conflict of Interest
Authors declare that there is no conflict of interest to reveal

References


