The role of phytocompounds in cancer treatment: A current review

Mohammed Shafi Sofi and Shabnum Nab

Abstract
Plant-derived products are considered excellent sources for the discovery and development of novel cancer chemo-protective and chemotherapeutic agents. Throughout medical history, plant products have been shown to be valuable sources of novel anti-cancer drugs. Several plant-derived compounds are currently successfully employed in cancer treatment, and many natural products have been tested against cancer and still there has been a long standing interest in the identification of medicinal plants and derived natural products for developing novel cancer therapeutics. There are more than 270,000 higher plants existing on this planet. But only a small portion has been explored phytochemically. So, it is anticipated that plants can provide potential bioactive compounds for the development of new ‘leads’ to combat cancer diseases. The activities of phytoconstituents from plant and the synergistic action shown by them with other drugs make them ideal in alternative cancer therapies. It was also known that nature is able to produce a wide variety of chemical entities of novel structure. Many of the new and novel compounds isolated from natural sources might otherwise have never been discovered, especially those of considerable complexity requiring the development of methods for the creation of new ring systems. On the basis of ethnobotanical knowledge, researchers are screening natural bioactive phytoconstituents from plant to identify bioactive compounds for the development of new therapeutic agents for the treatment of cancer this includes studies on secondary metabolites with chemopreventive, antiproliferative and cytotoxic activities. In this review, complete outlines of the natural bioactive anticancer phytoconstituents from plant are described. Further pharmaceutical developmental challenges and opportunities in bringing the phytochemicals into the market are also explored.

Keywords: anticancer bioactive phytoconstituents, cytotoxicity, cancer treatment

Introduction
Cancer is one of the most dreaded diseases of the 20th century and spreading further with continuance and increasing incidence in 21st century, an estimated 12.4 million people will be diagnosed with some form of cancer and around 7.6 million people will die [1]. As part of this global effort, many natural products have been tested against cancer cell lines [2] and still there has been a long standing interest in the identification of medicinal plants and derived natural products for developing cancer therapeutics [3]. Plants have been used as sources of medicinal agents since the beginning of mankind. As the age of modern medicine and single pure drugs emerged, plant-derived active principles and their semi-synthetic and synthetic analogs have served as a major route to new pharmaceuticals [4]. Human beings have relied on natural products as a resource of drugs for thousands of years. Plant-based drugs have formed the basis of traditional medicine systems that have been used for centuries in many countries such as Egypt, China and India [5]. Today plant-based drugs continue to play an essential role in health care. It has been estimated by the World Health Organization that 80% of the population of the world rely mainly on traditional medicines for their primary health care [6].

Natural anticancer phytoconstituents and their applications
Currently, over 50% of anticancer drugs approved by the US FDA are nature-derived [7] and over 60% of all drugs in clinical trials for cancers are nature related [8]. Epidemiological studies suggest that a reduced risk of cancer is associated with the consumption of a phytochemical-rich diet that includes fruits and vegetables [9]. Fresh and processed fruits and food products contain high levels of a diverse range of phytochemicals of which polyphenols including hydrolysable tannins (ellagitannins and gallotannins) and condensed tannins (proanthocyanidins) and anthocyanins and other flavonoids make up a large proportion [10]. Suggested mechanisms of anticancer effects of polyphenols include antioxidant,
anti-inflammatory and antiproliferative activities as well as their effects on subcellular signaling pathways, induction of cell-cycle arrest and apoptosis [11]. These phytochemicals generate much scientific interest, because they fulfill basic requirements of an ideal chemopreventive agent, such as selective toxicity to cancerous or precancerous cells, efficacy against most types of cancers, oral route of administration, and acceptance by target human population and have a known mechanism of action [12]. In 25 years, the National Cancer Institute (NCI) screened more than 120,000 plant extracts from 35,000 species for novel anticancer agents. Some promising discoveries are: taxol, indicine-n-oxide, phyllanthoside, and homoharringtonine, isolated from Taxus brevifolia Nutt., Heliotropium indicum L., Phyllanthus acurnnatus Vahl. And Cephalotaxus harringtonia Koch. etc. Natural products include: (1) an entire organism, (2) part of an organism, (3) an extract of an organism or part of an organism and exudates and (4) pure compounds (e.g. alkaloids, coumarins, flavonoids, glycosides, xanthones, lignans, phenylpropanoids, isoprenoids, sugars, etc, as illustrated in table- I) isolated from plants. Many of these compounds show a variety of biological and pharmacological activities and some of these compounds are essential for everyday life, both for humans and animals [13]. These agents have been found in fruits, vegetables, raisins, nuts, herbal extracts, and commonly consumed beverages such as wine, tea, and coffee [14, 15].

1. Alkaloids and their potential anticancer activities

The term ‘alkaloid’, is generally limited to organic bases formed in plants. By definition alkaloids contain nitrogen which is usually derived from amino acids. Because of the presence of a nitrogen atom, alkaloids react mostly alkaline and are able to form soluble salts in aqueous environments. In plants however they can occur in the free state, as a salt or as an N-oxide and they are accumulated in the plant vacuole as reservoir or often coupled to phenolic acids such as resorcin, and phenol. Many of these compounds are isolated from a variety of structural types isolated from plants, the alkaloids are divided into five major groups dependent on the nitrogen intermediates. Apoptosis seems to be the mode of action of the most potent of these alkaloids. Apoptosis is an essential mechanism for cells to die and be removed from the body. It plays a critical role in development, immune response, and elimination of pathogens.

Table 1: Natural anticancer Phytochemicals with their class, plant source and family.

<table>
<thead>
<tr>
<th>Sl.no.</th>
<th>Anticancer compound</th>
<th>Class</th>
<th>Plant Source</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Indicine N-oxide</td>
<td>Pyrrolizidines</td>
<td>Heliotropium indicum L.</td>
<td>Boraginaceae</td>
</tr>
<tr>
<td>2.</td>
<td>Thalicarpine</td>
<td>Aporphines</td>
<td>Thalictrum dysarcarpum Fisch.</td>
<td>Ranunculaceae</td>
</tr>
<tr>
<td>4.</td>
<td>Taxol</td>
<td>Taxaes</td>
<td>Taxus brevifolia Nutt.</td>
<td>Taxaceae</td>
</tr>
<tr>
<td>5.</td>
<td>Ellipticine</td>
<td>Alkaloid</td>
<td>Ochrosia elliptica Labill.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>6.</td>
<td>Nitidine and jagaronine</td>
<td>Benzophenon-thridines</td>
<td>Fagara macrophylla Lam.</td>
<td>Rutaceae</td>
</tr>
<tr>
<td>7.</td>
<td>3-Emethylocolchicine</td>
<td>Colchicine group</td>
<td>Colchicum spectosum Steven.</td>
<td>Colchicaceae</td>
</tr>
<tr>
<td>8.</td>
<td>Harringtonine and homoharringtonine</td>
<td>Cephalotaxus alkaloids</td>
<td>Cephalotaxus harringtonia Koch.</td>
<td>Drosaceae</td>
</tr>
<tr>
<td>9.</td>
<td>Tylocrebrine</td>
<td>Phenenthro-ucolizidines and</td>
<td>Tyllophora crebriflora Blake</td>
<td>Asclepiadaceae</td>
</tr>
<tr>
<td>10.</td>
<td>Emetine</td>
<td>Eccte group</td>
<td>Cephaelis acuminata Karst.</td>
<td>Rubicaceae</td>
</tr>
<tr>
<td>No.</td>
<td>Compound NAME</td>
<td>Class</td>
<td>Source Plant NAME</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>----------------</td>
<td>-------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Vinblastine/Vincristine</td>
<td>Indole alkaloid</td>
<td>Catharanthus roseus L.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>12.</td>
<td>Maquiroside A</td>
<td>Cardiac glycoside</td>
<td>Maquira calophylla (Poeppl. &amp; Endl.)</td>
<td>Moraceae</td>
</tr>
<tr>
<td>13.</td>
<td>Kamehanin</td>
<td>Diterpenoid</td>
<td>Rabdosia umbrosa var.</td>
<td>Lamiaceae</td>
</tr>
<tr>
<td>14.</td>
<td>Lariciresinol</td>
<td>Lignan</td>
<td>Wikstroemia elliptica Merr.</td>
<td>Thymelaeaceae</td>
</tr>
<tr>
<td>15.</td>
<td>3',4'-Deoxyxypyruspermin</td>
<td>Xanthone</td>
<td>Psorospermum febrifugum Spach.</td>
<td>Gentianaceae</td>
</tr>
<tr>
<td>16.</td>
<td>Larreantin</td>
<td>Quinone</td>
<td>Larrea tridentate Coville.</td>
<td>Zygophyllaceae</td>
</tr>
<tr>
<td>17.</td>
<td>Allamaridin</td>
<td>Monoterpenoid</td>
<td>Allamanda cathartica L.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>18.</td>
<td>Cadraicoslavone</td>
<td>Lignans</td>
<td>Cudrania cochinensis Lour.</td>
<td>Moraceae</td>
</tr>
<tr>
<td>19.</td>
<td>Helenalin</td>
<td>Sesquiterpenoid</td>
<td>Heliotropium indicum L.</td>
<td>Boraginaceae</td>
</tr>
<tr>
<td>21.</td>
<td>Colchicine</td>
<td>Alkaloid</td>
<td>Colchicum spectosum Steven.</td>
<td>Colchicaceae</td>
</tr>
<tr>
<td>22.</td>
<td>Umbelliferone</td>
<td>Coumarin</td>
<td>Wilskstroemia elliptica Merr.</td>
<td>Thymelaeaceae</td>
</tr>
<tr>
<td>23.</td>
<td>Epipodophyllumotoxin (etoposide and teniposide)</td>
<td>Alkaloids</td>
<td>Podophyllum species L.</td>
<td>Berberidaceae</td>
</tr>
<tr>
<td>25.</td>
<td>Acobioside A</td>
<td>Steriods lactones</td>
<td>A. oblongifoliv var.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>26.</td>
<td>Adheryn</td>
<td>Steriods lactones</td>
<td>Nerium oleander L.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>27.</td>
<td>Alkanin</td>
<td>Quinones</td>
<td>Arnebia nobilis Reich.</td>
<td>Boraginaceae</td>
</tr>
<tr>
<td>28.</td>
<td>a-amyrin</td>
<td>Triterpenes</td>
<td>Bursera schlechtendalii Engl.</td>
<td>Burseraceae</td>
</tr>
<tr>
<td>29.</td>
<td>Anacardic acid</td>
<td>Polyphenols</td>
<td>Anacardium occidentale L.</td>
<td>Anacardiaceae</td>
</tr>
<tr>
<td>30.</td>
<td>Aristolochic acid</td>
<td>Alkaloids</td>
<td>Aristolochia indica L.</td>
<td>Aristolochiaceae</td>
</tr>
<tr>
<td>32.</td>
<td>Betulin</td>
<td>Triterpenes</td>
<td>Alnus firmaflora Nutt.</td>
<td>Betulaceae</td>
</tr>
<tr>
<td>33.</td>
<td>Bruceantin</td>
<td>Quassinoids</td>
<td>Brucea antidysenterica Mill.</td>
<td>Simaroubaceae</td>
</tr>
<tr>
<td>34.</td>
<td>Calotropin</td>
<td>Steriods lactones</td>
<td>Asclepiascurassavica L.</td>
<td>Asclepiadaceae</td>
</tr>
<tr>
<td>35.</td>
<td>Campothecin</td>
<td>Alkaloids</td>
<td>Camptotheca acuminata Deene.</td>
<td>Nyssaceae</td>
</tr>
<tr>
<td>36.</td>
<td>Celsiside C</td>
<td>Saponins</td>
<td>Centaurea melitensis L.</td>
<td>Asteraeae</td>
</tr>
<tr>
<td>37.</td>
<td>Cerberin</td>
<td>Steriods lactones</td>
<td>Thevetia peruviana Pers.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>38.</td>
<td>Cusain</td>
<td>Proteins</td>
<td>Caesalpinia gilliesii Wall.</td>
<td>Fabaceae</td>
</tr>
<tr>
<td>39.</td>
<td>Colubrinol</td>
<td>Ansa macrolides</td>
<td>Colubrina texensis Torr.&amp;Gray</td>
<td>Rhamnaceae</td>
</tr>
<tr>
<td>40.</td>
<td>Copasine chloroide</td>
<td>Alkaloids</td>
<td>Chelidonium majus L.</td>
<td>Papaveraceae</td>
</tr>
<tr>
<td>41.</td>
<td>Flavopiridol</td>
<td>Flavonoid</td>
<td>Dysosolium binectariferum Hook.</td>
<td>Meliaceae</td>
</tr>
<tr>
<td>42.</td>
<td>Costanolide</td>
<td>Sesquiterpenes</td>
<td>Liriodendro tulpifera L.</td>
<td>Magnoliidae</td>
</tr>
<tr>
<td>43.</td>
<td>Crinamide</td>
<td>Alkaloids</td>
<td>Crinum macranthitrum Engl.</td>
<td>Amaryllidaceae</td>
</tr>
<tr>
<td>44.</td>
<td>Cryptopleurine</td>
<td>Alkaloids</td>
<td>Boehmeria-cylindrical L.</td>
<td>Urticaceae</td>
</tr>
<tr>
<td>45.</td>
<td>Cucurbitacin B</td>
<td>Cucurbitacins</td>
<td>Cucurbita digitata Gray</td>
<td>Cucurbitaceae</td>
</tr>
<tr>
<td>46.</td>
<td>Cucurbitacin glycos</td>
<td>Cucurbitacins</td>
<td>Datiscaquarnera Presl.</td>
<td>Datiscaeae</td>
</tr>
<tr>
<td>47.</td>
<td>Cycloedrine</td>
<td>Alkaloids</td>
<td>Ceclea pectiata L.</td>
<td>Menispermae</td>
</tr>
<tr>
<td>48.</td>
<td>Cymarin</td>
<td>Steriods lactones</td>
<td>Apocynum cannabinum L.</td>
<td>Apocynaceae</td>
</tr>
<tr>
<td>49.</td>
<td>Damsin</td>
<td>Sesquiterpenes</td>
<td>Ambrosia Ambrostoides Cav.</td>
<td>Asteraceae</td>
</tr>
<tr>
<td>50.</td>
<td>Demecolcinol</td>
<td>Alkaloids</td>
<td>Colchicumpectosum Steven</td>
<td>Liliaceae</td>
</tr>
<tr>
<td>51.</td>
<td>3-Demethylpodophyllumotoxin</td>
<td>Lignans</td>
<td>Linum album Kotschy ex Boiss.</td>
<td>Linaceae</td>
</tr>
<tr>
<td>52.</td>
<td>Deoxypodophyllumotoxin</td>
<td>Lignans</td>
<td>Burserafragaroidesvar.</td>
<td>Burseraceae</td>
</tr>
<tr>
<td>53.</td>
<td>Digitoxin</td>
<td>Steriods lactones</td>
<td>Digitalis purpurea L.</td>
<td>Scrophulariaceae</td>
</tr>
<tr>
<td>54.</td>
<td>Elephantopin</td>
<td>Sesquiterpenes</td>
<td>Elephantopuselatus Bertol.</td>
<td>Asteraceae</td>
</tr>
<tr>
<td>56.</td>
<td>Emodin(aloe-emodin)</td>
<td>Quinones</td>
<td>Rhamnus frangula L.</td>
<td>Rhamnaceae</td>
</tr>
<tr>
<td>57.</td>
<td>Erioflorin</td>
<td>Sesquiterpenes</td>
<td>Eriothylanlanatum (Pursh)</td>
<td>Forbes var.</td>
</tr>
<tr>
<td>58.</td>
<td>Eupatolin</td>
<td>Sesquiterpenes</td>
<td>Eupatorium canefolium Willd.</td>
<td>Asteraeae</td>
</tr>
<tr>
<td>59.</td>
<td>Eupatoroxin</td>
<td>Sesquiterpenes</td>
<td>Eupatorium rotundifolium L.</td>
<td>Asteraeae</td>
</tr>
<tr>
<td>60.</td>
<td>Fagarone</td>
<td>Alkaloids</td>
<td>Fagara zanthoxyloides Lam.</td>
<td>Rutaceae</td>
</tr>
<tr>
<td>61.</td>
<td>Fastilgin B.</td>
<td>Sesquiterpenes</td>
<td>Baileyanumradiata Harv. &amp; Gray</td>
<td>Asteraeae</td>
</tr>
<tr>
<td>62.</td>
<td>Gaillardin</td>
<td>Sesquiterpenes</td>
<td>Gaillardia pulchella Foug.</td>
<td>Asteraeae</td>
</tr>
<tr>
<td>63.</td>
<td>Gallic acid</td>
<td>Polyphenols</td>
<td>Oenothera canaspissa Nutt.</td>
<td>Onagraceae</td>
</tr>
<tr>
<td>64.</td>
<td>Glaucurabalone</td>
<td>Quinoids</td>
<td>Pteroevansendron kerstzii. Engl.</td>
<td>Simaropaeae</td>
</tr>
<tr>
<td>65.</td>
<td>Gossypol</td>
<td>Terpenoid</td>
<td>Gossypium hirsutum L.</td>
<td>Malvaceae</td>
</tr>
<tr>
<td>66.</td>
<td>Harringtonine</td>
<td>Alkaloids</td>
<td>Cephalotaxus harringtonia Koch</td>
<td>Cephalotaxaceae</td>
</tr>
<tr>
<td>67.</td>
<td>Helenalin</td>
<td>Sesquiterpenes</td>
<td>Helenium helenoides L.</td>
<td>Asteraeae</td>
</tr>
<tr>
<td>68.</td>
<td>Hyrcanoside</td>
<td>Steriods lactones</td>
<td>Coronilla varia L.</td>
<td>Fabaceae</td>
</tr>
<tr>
<td>69.</td>
<td>Indicine N-oxide</td>
<td>Alkaloids</td>
<td>Heliotropium indicum L.</td>
<td>Boraginaceae</td>
</tr>
<tr>
<td>70.</td>
<td>Isoicruceine B</td>
<td>Quassinoids</td>
<td>Brucea antidysenterica Lam.</td>
<td>Simaroubaceae</td>
</tr>
<tr>
<td>71.</td>
<td>Jatrophone</td>
<td>Diterpenes</td>
<td>Jatrophacacrora Benth.</td>
<td>Euphorbiaceae</td>
</tr>
<tr>
<td>72.</td>
<td>Lignin</td>
<td>Polyphenols</td>
<td>Jacaranda caucana Pittier</td>
<td>Bignoniaceae</td>
</tr>
<tr>
<td>73.</td>
<td>Maysine</td>
<td>Ansa-macrolides</td>
<td>Maytenus bucharanii Loes.</td>
<td>Celastraceae</td>
</tr>
<tr>
<td>74.</td>
<td>Myrsine saponin</td>
<td>Saponins</td>
<td>Myrsine africana L.</td>
<td>Myrsinaceae</td>
</tr>
<tr>
<td>75.</td>
<td>Nitinine chloride</td>
<td>Alkaloids</td>
<td>Fagara chalybea Engl.</td>
<td>Rutaceae</td>
</tr>
</tbody>
</table>
2. Phenolics and their potential anticancer activities

Recently, attention has been given to the chemopreventive and therapeutic effects of naturally occurring phenolic phytochemicals due to their anticancer potential. Phenolics are compounds possessing one or more aromatic rings with one or more hydroxyl groups. They are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants, with more than 8,000 phenolic structures currently known, ranging from simple molecules such as phenolic acids to highly polymerized substances and may inhibit the formation and growth of tumors by induction of cell cycle arrest and apoptosis [25]. Many plant-derived dietary polyphenols have been studied for their chemopreventive and chemotherapeutic properties against human cancers, including green tea polyphenols, genistein (found in soy), apigenin (celery, parsley), luteolin (broccoli), quercetin (onions), kaempferol (broccoli, grapefruits), curcumin (turmeric) [26]. The more we understand their involved molecular mechanisms and cellular targets, the better we could utilize these “natural gifts” for the prevention and treatment of human cancer. Furthermore, better understanding of their structure-activity relationships will guide synthesis of analog compounds with improved bioavailability, stability, potency and specificity. Phenolic extracts or isolated polyphenols from different plant food have been studied in a number of cancer cell lines including leukemia, lymphoma, prostate, breast, lung, head and neck cancer cells [36].

3. Flavonoids and their potential anticancer activities

Flavonoids constitute one of the most ubiquitous groups of all plant phenolics. So far, over 8,000 varieties of flavonoids have been identified in plants. Flavonoids are a sub-group of phenolic compounds characterized by a benzene ring A and a C 6-C 3-C 6 heterocyclic ring system. Depending on the presence or absence of hydroxyl and methoxyl groups at specific positions in ring B and ring C, flavonoids can be divided into several subclasses: flavones, flavanones, flavanols, isoflavones, and anthocyanidins. Flavonoids exhibit a wide range of biological activities, including antioxidant, anti-inflammatory, antimicrobial, and anti-cancer properties. They are considered to be potential chemopreventive agents against cancer due to their ability to suppress cell proliferation, induce cell death, and inhibit angiogenesis.

The presence of ellagic acid and ellagic acid derivatives in muscadine grapes is unique among the grape varieties, whereas it is abundantly present in a number of fruits and vegetables. Ellagic acid and its derivatives have been shown to exert anticarcinogenic activity by decreasing growth, inducing apoptosis, altering cell cycle kinetics, and interfering with intracellular signal transduction events in cancer cells [32; 33]. The presence of ellagic acid and ellagic acid derivatives in mussel and plant foods is unique among Vitis species, whereas it is a major compound in fruits such as blueberries, blackberries, raspberries, and cranberries [34]. The anticancer properties of free ellagic acid and polyphenolic extracts that contain ellagic acid were demonstrated in several studies [35] and also enhanced the anticancer activity of other polyphenolic compounds [33]. The great diversity of chemical types in this group of compounds are illustrated in table1, which lists the various flavonoids with their classes, their plant origin, and their scientific report. Other phenolic extracts or compounds intensively studies are from olives, legumes, citrus, apples, and also curcumin from spice turmeric. For example, soy isoflavone genistein can inhibit the growth of various cancer cell lines including leukemia, lymphoma, prostate, breast, lung, head and neck cancer cells [36].

27. Myrtus communis
28. Olea europaea
29. Oxydendron arboreum
30. Parthenocissus tricuspidata
31. Podophyllum peltatum
32. Podocarpus gracilior
33. Prunus serotina
34. Rubus idaeus
35. Rubus fruticosus
36. Rubus ulmifolius
37. Rubus idaeus laevigatus
38. Rubus ulmifolius
39. Rubus fruticosus
40. Rubus idaeus
41. Rubus ulmifolius
42. Rubus fruticosus
43. Rubus idaeus
44. Rubus ulmifolius
45. Rubus fruticosus
46. Rubus idaeus
47. Rubus ulmifolius
48. Rubus fruticosus
49. Rubus idaeus
50. Rubus ulmifolius
51. Rubus fruticosus
52. Rubus idaeus
53. Rubus ulmifolius
54. Rubus fruticosus
55. Rubus idaeus
56. Rubus ulmifolius
57. Rubus fruticosus
58. Rubus idaeus
59. Rubus ulmifolius
60. Rubus fruticosus
61. Rubus idaeus
62. Rubus ulmifolius
63. Rubus fruticosus
64. Rubus idaeus
65. Rubus ulmifolius
66. Rubus fruticosus
67. Rubus idaeus
68. Rubus ulmifolius
69. Rubus fruticosus
70. Rubus idaeus
71. Rubus ulmifolius
72. Rubus fruticosus
73. Rubus idaeus
74. Rubus ulmifolius
75. Rubus fruticosus
76. Rubus idaeus
77. Rubus ulmifolius
78. Rubus fruticosus
79. Rubus idaeus
80. Rubus ulmifolius
81. Rubus fruticosus
82. Rubus idaeus
83. Rubus ulmifolius
84. Rubus fruticosus
85. Rubus idaeus
86. Rubus ulmifolius
87. Rubus fruticosus
88. Rubus idaeus
89. Rubus ulmifolius
90. Rubus fruticosus
91. Rubus idaeus
92. Rubus ulmifolius
93. Rubus fruticosus
94. Rubus idaeus
95. Rubus ulmifolius
96. Rubus fruticosus
97. Rubus idaeus
98. Rubus ulmifolius
99. Rubus fruticosus
100. Rubus idaeus

Table 1: Summary of the main chemopreventive and chemotherapeutic properties of selected natural products.
have been identified [37]. Flavonoids occur as aglycones, glycosides and methylated derivatives [38]. In plants, flavonoids aglycones (i.e., flavonoids without attached sugar) occur in a variety of structural forms. All contain fifteen carbon atoms in their basic nucleus: two six-membered rings linked with a three carbon unit which may or may not be parts of a third ring [39]. Flavonoidic derivatives have a wide range of biological actions such as antibacterial, antiviral, anti-inflammatory, anticancer, and anti-allergic activities. Some of these benefits are attributed to the potent antioxidant effects of flavonoids, which include metal chelation and free-radical scavenging activities [40]. Flavopiridol is the most active of approximately 100 analogs when assayed against Cdkks and showed about 100-fold more selectivity compared to its activity vs tyrosine kinases. It showed roughly comparable activity in the 100–400 nM range for IC50 values, depending upon the specific Cdk. It was the first compound at NCI identified as a potential antitumor agent that subsequently was proven to be a relatively specific Cdk inhibitor [41]. The initial report [42] on its Cdk 2 inhibitory activity was made in 1994, followed by data demonstrating antitumor activity in 1995 [43]. Flavopiridol is currently in phase III clinical trials as an inhibitor of cyclin-dependent kinase 2 (Cdk2), both as a single agent and as a modulator in combination with other agents, particularly paclitaxel and cis-platinum. It has been reported to lead to partial and/or complete remissions in a number of phase I patients, leading to phase II studies in patients with paclitaxel-resistant tumors [44]. There have been a number of relatively recent reports of this agent and the various combinations with other drugs and drug candidates, a significant number of which are either natural products or derived from natural products [45]. Flavonoids are reported to inhibit specific enzymes, which include hydrodases, oxidoreductase, DNA syntheses, RNA polymerases, lipoygenase and glutathion s-transferase. They also block several digestive enzymes, including a-amylase, trypsin and lipase [46]. Many studies have shown that flavonoids inhibit PI3- kinase, protein kinase C, protein tyrosine kinase, and some transcriptional factors, and that such inhibition leads to cell growth arrest and tumor cell death [47; 48]. As a result, a rising number of authorized physicians are prescribing pure flavonoids to treat many important common diseases. It has been stated that flavonoids, as antioxidants, can inhibit carcinogenesis [49]. Some flavonoids—such as fisetin, apigenin, and luteolin—are stated to be potent inhibitors of cell proliferation. Furthermore, it has been speculated that flavonoids can inhibit angiogenesis [50]. Angiogenesis is normally a strictly controlled process in the human body. The process of angiogenesis is regulated by a variety of endogenous angiogenic and angiostatic factors. It is switched on, for example, during wound healing. Pathologic, unregulated angiogenesis occurs in cancer [51]. Angiogenesis inhibitors can interfere with various steps in angiogenesis, such as the proliferation and migration of endothelial cells and lumen formation. Among the known angiogenesis inhibitors, flavonoids seem to play an important role [52]. However, the mechanism behind the antiangiogenic effect of flavonoids is unclear. A possible mechanism could be inhibition of protein kinases. These enzymes are implicated to play an important role in signal transduction and are known for their effects on angiogenesis. Flavonoids found in litchi fruit pericarp (LFP) tissues extract exhibited potential in vitro and in vivo anticancer activity against hepatocellular carcinoma [53]. Furthermore, the LFP extract demonstrated a dose- and time-dependent inhibitory effect on cancer cell growth [54]. Anticancer activity of LFP extract on both positive and negative breast cancers could be attributed, in part, to its DNA damaging effect, proliferating inhibition and apoptosis induction of cancer cells through up-regulation and down-regulation of multiple genes involved in cell cycle regulation and cell proliferation, apoptosis, signal transduction and transcriptional regulation, motility and invasiveness of cancer cells [55]. The anticancer activity of the flavonols found in LFP tissues is similar to that of the anthocyanins. The anti-breast cancer activities of epicatechin, procyanidin B2, procyanidin B4 and the ethyl acetate fraction from LFP were examined. Procyanidin B4 and ethyl acetate fraction showed a stronger inhibitory effect on HELF than MCF-7 while epicatechein and procyanidin B2 had lower cytotoxicities towards MCF-7 and HELF than paclitaxel. It was suggested that epicatechin and procyanidin B2 can be employed as components of anti-breast cancer drugs [55]. Flavonoids varied significantly in their Antiproliferative potency depending on the structural features. Flavonoids of the flavone, flavonol, flavanone and isoflavone classes possess antiproliferative effects in different cancer cell lines. These natural compounds like flavonoids have several great advantages over other therapeutic agents. The natural, hemisynthetic and synthetic flavonoids alone or in combination with other preventive and/or therapeutic strategies will become effective future drugs against the most common degenerative diseases such as cancer, diabetes and cardiovascular complications [56].

4. Terpenoids and their potential anticancer activities

Terpenoids also referred to as terpenes, are the largest class of natural products constitute over 30,000 members [57; 58]. The classes of terpene compounds found in plants are monoterpenes, diterpenes, sesquiterpenes, triterpenes, tetraterpenes, and polyyterpenes. Terpenoid biosynthesis involves mostly head to tail addition of isopentenyl diphosphate (IPP, the active C5 isoprene unit), to its isomer dimethylallyl diphosphate (DAPP) synthesizing geranyl diphosphate (GPP, C10) [59]. These compounds are typically found in all parts (i.e. seed, flowers, foliage, roots and wood) of higher plants and also occur in mosses, liverworts, algae and lichens. Some are of insect or microbial origin. A number of dietary monoterpenes have antitumor activity, exhibiting not only the ability to prevent the formation or progression of cancer, but the ability to regress existing malignant tumors. Monoterpenes such as D-limonene and perillyl alcohol (POH) derived from orange peels and lavender, respectively, have been shown to possess chemopreventive properties against mammary, liver and lung carcinogenesis. It was reported, that the colon tumours of animals fed with POH exhibited increased apoptosis compared to those fed with control diet [60]. The cytotoxicity of diterpene taxol from Taxus brevifolia Nutt. (Taxaceae) represents both inhibition of cell proliferation and cell death. Over 100 different taxanes have been characterized from various Taxus species. The drug block cells in the G2/M phase of the cell cycle and induced apoptosis [61]. In lower concentration range, taxol stabilized the spindle during mitosis and this mitotic block led to the inhibition of cell proliferation and induction of apoptosis. In higher concentration range, taxol mainly increased the polymerization of microtubule and stimulated the formation of microtubule bundles which blocked entry into S phase and this led to the inhibition of cell proliferation and induction of necrosis [62]. Cell death induced by paclitaxel, on the other hand, occurs via a signalling pathway independent of
microtubules and G2/M arrest [63]. Paclitaxel is currently used to treat ovarian, lung, and breast cancers, head and neck carcinoma, and melanoma. It has been hailed as the perhaps most important addition to the chemotherapeutic armamentarium against cancer over the past several decades [64]. Limonene is a well-established chemopreventive and therapeutic agent against many tumor cells [65]. Carvone, a major monoterpene in caraway seed oil, has been shown to prevent chemically induced lung and forestomach carcinoma development [66]. In addition, carveol has chemopreventive activity against rat mammary cancer during the initiation phase [67]. The mechanism of action of monoterpens against tumor cells is the induction of apoptosis and interference of the protein prenylation of key regulatory proteins [68]. Among other halogenated acyclic monoterpens, halomarin, isolated from the red alga Portieria hornemanni [69], is very effective against renal, brain, colon, and non-small cell lung cancer cell lines through a unique mode of action [70]. Illudins are a family of natural toxic sesquiterpene compounds with antitumoractivity, isolated from the basidiomycete Omphalotus illudens (O. olearius and Clitocybe illudens). These compounds are believed to be responsible for the poisoning that occurs when Omphalotus is mistaken for an edible mushroom [71]. Illudins S and M are extremely cytotoxic and exhibit antitumor activity [72]. Irofulven is effective against various types of tumor cells at picomolar to nanomolar concentrations. A variety of multidrug-resistant tumor cell lines remain sensitive to the illudins [73]. Irofulven (hydroxymethylacylfulvene), a derivative of illudin S, has been extensively investigated and is currently in phase II clinical trials. In particular, irofulven exhibits efficacy against pancreatic carcinoma, a malignancy that is resistant to all other forms of chemotherapy. Irofulven rapidly enters cancer cells, where it binds to cellular macromolecules and inhibits DNA synthesis [74]. The most unique aspect of irofulven’s anticancer activity seems to be its ability to act as a selective inducer of apoptosis in human cancer cell lines, and, in contrast to conventional antitumor agents, this activity of irofulven is effective against tumor cell lines regardless of their p53 or p21 expression [75]. In addition, the DNA lesion induced by illudins and irofulven is largely ignored by global repair pathways. Therefore, the irofulven and other illudins are considered a new and promising class of tumor-therapeutic agents [76]. Terpenoid-derived drugs have contributed significantly to human disease therapy and prevention. Some terpenoid drugs have provided tremendous benefits for patients and for the pharmaceutical industry. Artemisinin and its derivatives comprise a multimillion-dollar market worldwide. Taxol alone is estimated to have annual sales of over $1.8 billion. Terpenoids indubitably continue to be important compounds for drug discovery.

5. Tannins and their potential anticancer activities
Tannins, phenolic phytochemicals, which are natural constituents of green tea, are considered to have cancer preventive properties [77, 78]. Condensed tannins, isolated from black beans, did not affect the growth of normal cells, but induced cell death in cancer cells in a dose-dependent manner. This cell death was associated with a concentration-dependent decrease of ATP and a deterioration of cellular gross morphology [79]. Tannins are types of plant polyphenols widely distributed in the plant kingdom that have been recently found to possess remarkable antitumor-promoting effects in various animal models and tumor systems [80]. Some tannin-related compounds, e.g. tellimagrandin II, remurin B, nobotanin A, nobotanin F, rugosin D, oenothein A, woodfordin D, nobotanin C, woodfordin F and nobotanin K from different plant sources induced cytotoxicity and inter-nucleosomal DNA cleavage in HL-60 cells. Their activity increased with polymerization when their concentration was expressed on a molar basis [81]. Classically, tannins are divided into two chemically and biologically distinct groups: the condensed tannins (CTs) also referred to as proanthocyanidins, and the hydrolyzable tannins (HTs) [82]. There is interest in proanthocyanidins because of their potential health benefits. Recent interest in these food polyphenols has emerged because of their antioxidant, free radical-scavenging, and metal-chelating activities, which may lead to their possible role in the treatment and prevention of cancer and other pathologies [83]. Several hydrolyzable tannins (HTs) and condensed tannins (CTs) have been found to block the activities of many mutagens and to have anticarcinogenic effects. When applied topically, injected, or added to the diet or drinking water, tannins were found to inhibit tumor initiation and carcinogenesis in the skin and the mammary gland [84]. The protective effects of tannins against many types of cancers lead us to postulate that these polyphenols are universal antitumor agents [85].

6. Phytosterols and their potential anticancer activities
Phytosterols are specific phytochemicals that resemble cholesterol in structure but are found exclusively in plants. Phytosterols have been studied both for their cholesterol lowering effects and their anticancer properties [86]. The most common phytosterols in the human diet are b-sitosterol, campesterol, and stigmasterol. Phytosterols are derivatives of the parent molecule 4-desmethyl sterol [87]. Phytosterols exist within plants in both esterified and free alcohol forms, more than 200 phytosterols exist naturally in the plant kingdom and many are found in edible foodstuffs [88]. Phytosterols in the diet are associated with a reduction in common cancers including cancers of the colon, breast, and prostate [89]. It was also showed that a 2% b-sitosterol mixture (95% b-sitosterol, 4% campesterol, and 1% stigmasterol) in the diet reduced to one-third the incidence of observable colon tumors induced by intracolonic administration of N-methyl-N-nitrosourea (MNU). Reduction in both the size of the proliferative compartment as well as the colonocyte labeling index within crypt columns in MNU-treated rats that were maintained on a diet containing 0.2% b-sitosterol [90]. Similarly in mice fed diets supplemented with phytosterols (0.3–2%), there was observed a dose-dependent reduction in cholic acid-induced colonic cell proliferation [91]. In similar experiments, using ovariec-tomized athymic mice that were injected with the MCF-7 estrogen receptor positive human breast cancer cells, a 32–42% reduction in tumor size was observed in mice fed diets enriched in b-sitosterol [92]. Potential protective effect of phytosterols against proliferation and metastasis of PC-3 human prostate cancer cells in male SCID mice was examined [93]. At the end of the 8 wk feeding period, there was a 40–43% reduction in tumor size in animals fed the phytosterol diet versus the cholesterol diet and a 50% reduction in the rate of tumor metastasis to the lungs, liver, and lymph nodes compared to those fed the cholesterol diet [86]. Phytosterols also affect cell cycle kinetics. In tissue culture studies of MDA-MB-231 human breast carcinoma cells, b-sitosterol induced cell cycle arrest at the G2/M transition [94]. Significant induction of cellular apoptosis following b-sitosterol supplementation has been observed in MDA-MB-231 hormone-insensitive human breast adenocarcinoma cells,
in metastatic LNCaP hormone-sensitive human prostate adenocarcinoma cells, in HT-29 human colon adenocarcinoma, and in PC-3 hormone-insensitive human prostate adenocarcinoma cells [95]. Other phytosterols including diosgenin and solamargine are potent inducers of apoptosis in human erythroblasts, HEL and K562 cell lines and human hepatocytic Hep3B cells [96].

7. Lignans and their potential anticancer activities
Lignans are a large group of phenolic compounds defined as dimers of phenylpropane (C6C3) units. This widely spread group of natural products possess a long and remarkable history of medicinal use in the ancient cultures of many people’s [97]. The first unifying definition of lignans was made by R. D. Howarth in 1936, who described them as a group of plant phenols with a structure, determined by the union of two aromatic rings, a long chain of carbon atoms, and an ether bond to a sugar side chain. Saponins exhibited three main types. They consist of a polycyclic aglycone that was used historically as soap (Latin saponaria), and an ether bond to a sugar side chain. Saponins are glycosides with a distinctive foaming characteristic. They are found in many plants can provide hydrophilic character.

8. Saponins and their potential anticancer activities
Saponins are glycosides with a distinctive foaming characteristic. They are found in many plants, but get their name from the soapwort plant (Saponaria), the root of which was used historically as soap (Latin sapo → soap). According to the structure of the aglycone or sapogenin, two kinds of saponins are recognised – the steroidal and the pentacyclic triterpenoid types. They consist of a polycyclic aglycone that is either a choline steroid or triterpenoid attached through C3 and an ether bond to a sugar side chain. Saponins exhibited many different biological and pharmacological actions such as immunomodulatory, antitumor, antiinflammatory, molluscicidal, antiviral, antifungal, hypoglycemic, hypcholesterolemic [102]. Saponins have a diverse range of properties, which include sweetness, bitterness foaming, emulsifying and haemolytic properties. Saponins have wide applications in beverages and confectionery, as well as in cosmetics and pharmaceutical products. They are believed to form the main constituents of many plant drugs and folk medicines, and are considered responsible for numerous pharmacological properties [103]. Notably, saponins can activate the mammalian immune system, which has led to significant interest in their potential as vaccine adjuvants [104].

9. Quassinoids and their potential anticancer activities
Quassinoids possess a wide spectrum of biological activities, some of which have been well researched and documented. According to their basic skeleton, quassinoids are categorized into five distinct groups, C-18, C-19, C-20, C-22 and C-25 types [112]. Many of these quassinoids display a wide range of biological activities in vitro and/or in vivo, including antitumor, antimarial, antiviral, anti-inflammatory, antifeedant, insecticidal, amoebicidal, antulcer and herbicidal activities [113]. At the present, quassinoids are found solely in various species of the Simaroubaceae family, such as Brucea antidysenterica, Brucea javanica, Simaba amara, Picrasma ailanthoides, Pierroedendron kerstingii, and Ailantluts grandi. All of these species belong to the Simarouboidae subfamily of Simaroubaceae, and some, in particular, have been used clinically for centuries. Originally, the collective bitter substances contained in such plants were termed quassin, after a man by the name of Quassi, who treated fever with the bark of these plants [113]. The research and application of quassinoids continued to extend through the 1990’s with the isolation and structure elucidation of many new compounds. Today, over 150 quassinoids have been isolated and fully characterized, and dozens of them have been found that do not fall into any of the basic quassinoid skeletal configurations the antitumor activity is one of the most impressive medicinal properties of quassinoids and has been well researched [114]. Many quassinoids display antitumor activity in different potencies. Bruceantin, brucantinol, gluazarubinone and simalkalacton D are among the most potent. The mechanism of the action is believed to be that quassinoids can inhibit the protein synthesis by inhibition of the ribosomal peptidyl transferase activity leading to the termination of the chain elongation [115]. Bruceantin, a quassinoid isolated from Brucea antidysenterica (Simaroubaceae), is a potent anticancer compound that decreased the growth of LLC cells. Its primary mechanism of action is the inhibition of protein synthesis [116].

Conclusion
Natural products discovered from medicinal plants have played an important role in the treatment of cancer. From the approximately 250000–300000 plants all over the world, only a small portion has been systematically investigated for the presence of bioactive phytochemicals. So, it is anticipated that plants can provide potential bioactive compounds for the
development of new ‘leads’ to combat cancer diseases. In this literature review, all the natural products experimentally studied showed some kind of pharmacological activity which could explain their capacity to act against cancer development. Also in this review, the data on 100 ethnomedical plants have been listed which are enumerated in table-I. These plants are still used traditionally as herbal drugs against various tumors such as sarcoma, lymphoma, carcinoma, and leukemia. Although these studies tend to support the use of these plant products on an experimental basis carried out in vitro and in vivo, in animals, in humans and in human cancer cell lines, their use will require clinical evaluation. In this literature review, all the natural products experimentally studied showed some kind of pharmacological activity which could explain their capacity to act against cancer development. The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. Experimental agents derived from natural products are offering us a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action. To conclude, it must be accepted that medicinal herbs have rich anticancer potential. They have shown anticancer activity in animal models of leukemia, skin cancer and sarcomas. Selected plants has been explored for biological activity and further investigations into anticancer activity of the plants, must be undertaken. The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. Experimental agents derived from natural products are offering us a great opportunity to evaluate not only totally new chemical classes of anticancer agents, but also novel and potentially relevant mechanisms of action.

References


63. Fan W. Possible mechanisms of paclitaxel-induced...


103. Liu J, Henkel T. Traditional Chinese medicine (TCM) are polyphenols and saponins the key ingredients triggering biological activities. Current Medicinal Chemistry. 2002; 9:1483-5.


