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Review

Natural products: New anti-cancer agents derived from plants

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ABSTRACT

Plants are a source of biologically-active compounds. They are used as crude material or pure compounds for cancer treatment. Besides these uses, such products are part of the integrative healthcare systems. Medicinal plants are formulated in different modern dosage forms, such as Cat's claw (*Uncaria tomentosa*), Maca (*Lepidium meyenii*), Dragon's blood (*Croton lechleri*), Acai palm (*Euterpe oleracea*), Noni (*Morinda citrifolia*) and Green tea. However, the use of medicinal plants in combination with conventional chemotherapeutics has significantly incremented the risk for adverse effects. Clinical data on interactions of medicinal plants with anti-cancer drugs contribute to the inter-individual variation, unexpected toxicities, and under-treatment seen in cancer patients. Based on the traditional use, or as part of systematic studies in the laboratory, plants and molecules with antitumor properties were studied; some of these plants are *Calophyllum brasiliense* and *Garcinia mangostana*, belonging to the family Clusiaceae. Juice of *G. mangostana* is sold as a dietary supplement with chemopreventive properties. Its effects are mainly attributed to xanthones, which inhibit cell proliferation, affect signaling pathways and induce apoptosis in different cell lines. Other xanthones are also present in *C. brasiliense* and are currently under study to determine their antitumor properties. All these features of xanthones make these compounds excellent candidates as anti-cancer agents and to study novel mechanisms of action that can be exploited as new therapeutic targets with fewer side effects, improve the patient's quality of life and reduce costs in public and private health systems.

KEYWORDS: active principles, antineoplastic agents, xanthones

ABBREVIATIONS

BPH: Benign prostate hyperplasia, CML: Chronic myelogenous leukemia, FL: Follicular lymphoma, NSCLC: Non-small cell lung cancer

INTRODUCTION

Mexico is one of the five megadiverse countries of the world given that about 50% of the 30,000 vascular plants species are endemic [1]. Over 3000 of these plants are used medicinally; it is 10% of the total floristic richness of the country [2]. Currently, in Mexico, there are about 4,000 species with medicinal attributes (15% of the total flora). This number coincides with that reported in several regions of the world from specialists in this subject, who believe that one in every seven species has a healing property.

The interest in knowing the properties of plants is related with the need to find ways of alleviating illness, injury, suffering and other symptoms. In Mexico, this interest in learning about phytotherapeutic resources dates back to pre-Conquest times. As examples we can point to the old botanical gardens, among which are the

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Cerro de Tetzcotzingo in the kingdom of Texcoco, and Quauhnahuac Oaxtepec Huaxtepetl in Cuernavaca [3]. The Codex de la Cruz-Baldiano (from 1552) collects most of those traditions from indigenous medicinal herbs. Since then, several studies have been made in order to establish therapeutic uses of medicinal plants in Mexico, based on adequate dosage and preparation [2].

The discovery of new drugs from medicinal plants may be aided by ethnopharmacology, which is a mode of scientific investigation of the indigenous' medicinal uses of various species (Table 1). Fabricant and Farnsworth, in 2001, documented 122 plant natural products with therapeutic use in their pure form, of which over 70% were developed, at least partially, as a consequence of the gathering of available ethnopharmacological information [4].

Modern medicine from plants

Currently, an estimated 80% of the world's population uses traditional herbal medicine for primary health care. In Asia, millions of people maintain their health through the use of leaves, roots and bark. In fact, 25% of medicines prescribed by European physicians and the United States are derived from plants found in forests. According to leading researchers, almost all these plants have been "discovered" thanks to the information derived from its use in traditional medicine [5] [6]. In Mexico, chronic degenerative diseases are a public health problem, with cancer as the third cause of death in the population and the leading cause of morbidity, involving the biggest health-related expense. Among the cases of morbidity from cancer, leukemia had the greatest number of cases in 2007 (13.2% in women and 19.4% in men) [7].

Treatment strategies for several types of cancers are basically surgery, radiotherapy and chemotherapy. The latter two currently used conventional treatments (Table 2) are expensive, have unwanted side effects, reduce the quality of life and often involve other health-related complications. This discourages the patients to continue with their treatments and, therefore, results in a low success rate. On the other hand, surgical procedures generate functional deficiencies or esthetic discomfort. Therefore it is necessary to develop new drugs that can be used in a wider variety of cancers, that are more selective against tumor cells, that induce fewer side effects, and are hopefully, easy to obtain. The obvious source of these compounds turns out to be plant-derived compounds [8].

Plant-derived anti-cancer agents in clinical use

There are now four major structural classes of plant-derived compounds used in medicine as single chemical entity compounds, namely, the vinca alkaloids (vinblastine, vincristine, vinorelbine), the epipodophyllotoxin lignans (etoposide, teniposide, etoposide phosphate), the taxane diterpenoids (paclitaxel, docetaxel), and the camptothecin quinoline alkaloid derivatives (toptotecan, irinotecan), as listed in order of their introduction to established oncology therapy in the United States [9] (Table 2). Since a detailed treatment of these four classes of plant-derived agents has appeared in the literature recently [10], these compounds will not be further discussed in the present review. However, it should be noted that the contributions of pioneering natural product chemists in North American academic, governmental, industrial, and private research institutions were instrumental in the isolation and/or structure elucidation of the key lead compounds vinblastine, vincristine, podophyllotoxin, taxol, and camptothecin. The antineoplastic activities of these five compounds were discovered through systematic laboratory studies, rather than relying on ethnomedical observations on their respective plants of origin [4].

New sources of anti-cancer drugs

Although plants have been used for over 3,500 years in the treatment of "cancer", it was only since the late 1950s that the evaluation of crude plant extracts for their antiproliferative potential was initiated in earnest. Since then, more than 120,000 plant extracts from over 6,000 genera have been tested, resulting in the development of a large number of widely structurally divergent "natural products" as candidate anti-cancer agents (Table 3). Some of these proved to be clinically useful, and others served as tools to unravel the biochemical mechanisms involved in the growth and regulation of tumors. In the latter cases, a broad arsenal of mechanisms of action has been

Table 1. Ethnomedicinal uses of Mexican plants employed empirically.

Disease	**Medicinal Plant**
Arthritis and others	*Larrea divaricata, Larrea mexicana, Larrea tridentata, Zygophyllum tridentatum* [47].
Cancer	*Acalypha califórnica,* Aeschynomene fascicularis, *Aloe vera, Bonellia macrocarpa, Bouganinvillea glabra, Cirsium mexicanum, Croton alamosanum, Hippocratea excelsa, Justicia spicigera, Krameria erecta, Lophocereus schotti, Magnolia dealbata, Pedilanthus tithymaloides, Persea americana, Psaccallium sp, Rhoeo discolor, Ruta chalepensis, Solanum ptychanthum, Tourrnefortia hartwegiana, Tradescantia spathaceae* [48-55].
Cardiovascular	*Agastache Mexicana, Agave atrovirens, Casimiroa edulis, Chenopodium murale, Chirantodendrom pentadactylon, Drococephalum moldavica, Lepechina caulesens, Epling sp, Myrica cerifera, Ocimum basilicum, Phleboduim aureum, Prunus serotina ssp capuli, Psittacanthus calyculatus, Ruta chalepensis, Sechium edule* Sw. [52, 56, 57].
Diabetes	*Acosmium panamense, Agave ixtli, Aloe vera, Azadirachta sp, Bidens pilosa, Buddleia cordata, Catharantus roseus, Cecropia obtusifolia, Ceiba aesculifolia subsp. Parvifolia, Celea zacatechichi, Cirsium mexicanum, Citrus aurantifolia, Cnidoscolus aconitifolius, Costus spicatus, Cuscuta corymbosa, Equisetum myriochaetum, Eryngium longifolium, Lantana cámara, Larrea divaricata, Larrea mexicana, Lepechina caulensens, Lophocereus schotii, Malmea depressa, Marrubium vulgare, Opuntia ficus indica, Opuntia fuliginosa, Opuntia hyptiacantha, Opuntia lasciacantha, Opuntia streptacantha, Pedilanthus tithymaloides, Physialis virginiana, Platanus mexicana, Psaccallium sp, Pteridium aquilinum, Quercus resinosa, Salvia aff, Amarissima sp, Sechium edule, Tecoma stans, Tourrnefortia hartwegiana* [47-49, 52, 53, 58-60].
Digestive	*Catharantus roseus, Dyssodia pinnatum, Ocimum bacilicum* [8].
Gastrointestinal ailments (including gastritis)	*Acacia macracantha, Acalypha califórnica, Aloe vera, Amphyipterygium adstrigens, Annona cherimota, Artemisia ludoviciana ssp mexicana, Byrsonima crassifolia, Calendula officinalis, Celea ternifolia, Chamaesyce hirta, Chamomilla recutita, Cissus verticillata, Croton alamosanus, Cuphea aequipetala, Guaiacum coulteri, Krameria cytisoides, Krameria erecta, Lepechinia caulescens, Lepidium virginicum, Lopezia racemosa, Ludwigia repens, Lysiloma acapulcense, Matricaria recutita, Menta x piperita, Moussania deppeana, Packera, candidissima, Persea americana, Pithecellobium dulce, Proboscidea fragans, Prosopis juliflora, Pseudognaphalium viscosum, Quercus rugosa, Randia echinocarpa, Salix bonplandiana, Sphaeralcea angustifolia, Tournefortia densiflora, Verbena Carolina* [47, 48, 61].
Infections	*Amphypteringium adstrigens, Castella tortuosa, Coutarea latiflora, Ibervillea sonorae, Jatropha cuneata, Luffa aegyptiaca, Selaginella lepidophylla* [53, 62].
Central nervous system disorders	*Ternstroemia pringlei* [63].
Gastrointestinal inflammation	*Acacia angustissima, Ambrosia confertiflora, Bignonia unguis-cati, Malva parviflora, Milleria quinqueflora* [50].
Gynecological disorders	*Psidii guajavae folium* [64].
Hypertension	*Bougainvillea glabra, Ruta chapalensis, Sambucus mexicans, Taraxacum officinale, Tila mexicana* [52].

Table 1 continued..

Intestinal infections (diarrhea)	*Acacia farnesiana, Acalypha adenostachya, Acalypha monostachya, Anemopsis califórnica, Annona cherimola, Bocconia frutescens, Caesalpinia pulcherrima, Chenopodim álbum, Chenopodium ambrosioides, Chrysactinia mexicana, Cuphea pinetorum, Diphysa minutifolia, Dorstenia contrajerva, Galium mexicanum, Geranium mexicanum, Hedeoma drummondii, Helianthemum glomeratum, Jacaranda mimisifolia, Karwinskia humboldtiana, Laelia anceps, Lipia alba, L. dulcis, L. graveolens, Lygodium venustums, Montanoa tomentosa, Ocimum bacilicum, Petiberia alliaceae, Physalis coztomatl. Piper umbellatum, Poliomintha longiflora, Psidium guajava, Punica granatum, Rubus coriifolius, Rumex crispus, Ruta chalepensis, Satureia laevigata, Schinus molle, Senna villosa, Solanum ptychanthum, Tribulus cistoides, Waltheria indica* [52, 53, 58, 65-74].
Intestinal parasites	*Asclepias albicans, Chenopodium ambrosioides, Eupatorium collinum, Euphorbia hirta, E. plicata, E. schlechtendalii, Heliotropium angiospermum, Larrea tridentata, Lobelia laxiflora, Marrubium vulgare, Melochia nodiflora, Plantago major, Potentilla thurberi, Teucrium cubense* [50, 73].
Renal infections	*Arctostaphylos pungens, Commelina longicaulis, Dyssodia pinnata, Equisetum hyemale, Medicago sativa* [58].
Rheumatism	*Allium sativum, Phlebodium aureum, Sphaeralcea angustifolia* [52].
Skin infections/wounds	*Ageratum houstonianum, Aloe vera, Mimosa tenuiflora* [52, 75].
Vermifuge	*Allium sativum, Dysphania ambrosioides, Mentha spicata, Mentha x piperita* [52].

Table 2. Current chemotherapeutic drugs clinically used.

Compound	**Plant**	**Cancer type**
Elliptinium	*Bleekeria vitensisi*	Breast [6].
Campthethecin Irinotecan Topotecan	*Camptotheca acuminata*	Ovarian, Small cell lung, Colorectal [11].
Vinca alkaloids: Vinblastine Vincristine Vindesine Vinolrelbine	*Catharanthus roseus*	Leukemia, Lymphoma, Advanced testicular cancer, Breast, Lung, Kaposi´s sarcoma [76].
Harringtonine Homoharringtonine	*Cephalotaxus harringtonia*	Acute myelogenous leukemia, Chronic myelogenous leukemia [11].
Epipodophyllotoxin: Etoposide Teniposide	*Podophyllum emodii, P. peltatum*	Lymphoma, Bronchial, Testicular [77].
Taxanes: Docetaxel (Taxotere) Paclitaxel (taxol)	*Taxus baccta T. brevifolia* *T. canadensis*	Breast, Ovarian, Non-small cell lung cancer (NSCLC), Kaposi's sarcoma [11].

Table 3. Different plants used to treat specific types of cancer.

Cancer Type	Scientific name
Breast	*Amphipterygium adstringens, Annona muricata, Annona purpurea, Betula platyphylla, Bidens pilosa, Bursera bipinnata, Bursera copallifera, Camellia sinensis, Cestrum nocturnum, Cordia curassavica, Cyathostemma argentium, Dendropanax arboreus, Diospyros digyna, Garcinia mangostana, Helianthella quinquenervis, Hypericum silenoides silenoides, Ibervillea sonorae, Lophophora williamsii, Magnolia officinalis, Melampodium paniculatum, Melandrium firmum, Mosannona depressa, Neurolaena lobata, Pancratium littorale, Persea americana, Senna occidentalis, Tagetes lucida, Tecoma stans, Thevetia ahouai, Tithonia diversifolia, Trifolium pretense, Zea mays* [8, 78-83].
Bladder	*Camellia sinensis, Trifolium pretense* [78].
Cervix	*Acacia pennatula, Acaciella angustissima, Agave salmiana, Amphipterygium adstringens, Bidens pilosa, Bocconia frutescens, Camellia sinensis , Capraria biflora, Cladocolea grahamii, Colubrina macrocarpa, Cuphea aequipetala, Dioon spinulosum, Galphimia glauca, Gossypium hirsutum, Hamelia patens, Havardia albicans, Hintonia latiflora, Hippocratea excelsa, Hyptis suaveolens, Ibervillea sonorae, Iostephane heterophylla, Ipomoea wolcottiana wolcottiana, Juniperus deppeana, Justicia spicigera, Linum scabrellum, Montanoa leucantha, Pachycereus webery, Pentalinon andrieuxii, Persea Americana, Phaseolus acutifolius, P. vulgaris, Phoradendron galeottii, P. reichenbachianum, Piper aduncum, Rhizophora mangle, Schkuhria schkuhrioides, Senna racemosa, Solanum rostratum, Tagetes lucida, Viburnum jucundum, Viguiera decurrens* [8, 78-80, 84].
Colorectal	*Adenophyllum aurantium, Ambrosia monogyra, Aristolochia brevipes, A. montícola, Asclepias subulata, Baccharis salicifolia, Begonia heracleifolia, Bidens pilosa, Bursera fagaroides, Crescentia alata, Curcuma longa, Descurainia pinnata, Dorstenia drakena, Elytraria imbricata, Epaltes rellana, Ganoderma lucidum, Gnaphalium purpureum, Haplopappus spinulosus scabrellus, Heliotropium curassavicum, Justicia spicigera, Krameria pauciflora, Manilkara zapota, Pectis haenkeana, Phoradendron carneum, Psittacanthus calyculatus, Tradescantia zebrina, Xanthosoma robustum, Xylotamia diffusa, Zea mays* [8, 78, 85].
Colon	*Acacia pennatula, Agave salmiana, Amphipterygium adstringens, Annona purpurea, Bursera bipinnata, B. copallifera, Cladocolea grahamii, Colubrina macrocarpa, Cuphea aequipetala, Curcuma longa, Galphimia glauca, Helianthella quinquenervis, Hippocratea excels, Hyptis suaveolens, Iostephane heterophylla, Ipomoea wolcottiana, Linum scabrellum, Manilkara zapota, Mosannona depressa, Panax ginseng, Pentalinon andrieuxii, Persea americana, Phoradendron galeottii, P. reichenbachianum, Schkuhria schkuhrioides, Smallanthus rellana, Solanum lanceolatum, Viburnum jucundum, Viguiera decurrens, Zea mays* [8, 78, 81].
Esophageal	*Camellia sinensis, Magnolia officinalis* [78, 82].
Fibrosarcoma	*Bursera graveolens* [8].
Fibroblastoma	*Lophophora williamsii* [8].
Gastric	*Alnus jorullensis, Annona muricata, Bocconia frutescens, Capsicum annum, Castela tortuosa, Chrysophyllum mexicanum, Columbrina macrocarpa, Dioon spinulosum, Helianthella quinquenervis, Heliotropium curassavicum, Hintonia latiflora, Hippocratea excels, Hyptis emory, Krameria pauciflora, Lanatana urticifolia, Larrea tridentata, Manilkara zapota, Salvia pachyphylla, Smallanthus varian, Smilax aristolochiifolia, Tagetes lucida, Trasdescantia zebrine, Verbesina persicifolia, Viburum jucumdum, Viguiera decurrens, V. hypargyrea, V. lactibracteata, V. quinqueradiata, Zea mays* [8, 86, 87].

Table 3 continued..

Glioma	*Amphipterygium adstringens, Annona muricata, Bocconia frutescens, Cestrum nocturnum, Cordia curassavica, Dendropanax arboreus, Diospyros digyna, Hypericum silenoides, Jatropha neopauciflora, Melampodium paniculatum, Neurolaena lobata, Pachycereus webery, Petiveria alliacea, Piper aduncum, Senna occidentalis, Thevetia ahouai, Tithonia diversifolia* [8].
Head	*Camellia sinensis* [88].
Hepatocarcinoma	*Tecoma stans* [8].
Kidney	*Acaciella angustissima, Annona purpurea, Dioon spinulosum, Gossypium hirsutum, Hamelia patens, Havardia albicans, Persea americana, Rhizophora mangle, Senna racemosa, Tradescantia discolor, Trifolium pretense* [78].
Laryngeal	*Acaciella angustissima, Cuphea aequipetala, Gossypium hirsutum, Hamelia patens, Havardia albicans, Rhizophora mangle, Senna racemosa, Tradescantia discolor* [8].
Leukemia	*Amphipterygium adstringens, Astianthus viminalis, Bocconia frutescens, Camellia sinensis, Castela tortuosa, Cladocolea grahamii, Euphorbia pulcherrima, Heterotheca inuloides, Hintonia latiflora, Hyptis pectinata, H. verticillata, Ipomoea pauciflora, Jacaranda mimosifolia, Jatropha neopauciflora, Lophophora williamsii, Magnolia officinalis, Montanoa leucantha, Petiveria alliacea, Pfaffia paniculata, Phoradendron galeottii, P. reichenbachianum, Piper aduncum, Plumbago pulchella, Psidium guajava, Solanum chrysotrichum, Tecoma stans, Trifolium pretense, Viguiera decurrens, Zea mays* [8, 82, 83].
Lung	*Alstonia scholaris, Annona muricata, A. purpurea, Camellia sinensis, Casearia sylvestris, Cestrum nocturnum, Cordia curassavica, Dendropanax arboreus, Dioon spinulosum, Diospyros digyna, Helianthella quinquenervis, Hypericum silenoides, Magnolia officinalis, Melampodium paniculatum, Mosannona depressa, Neurolaena lobata, Persea americana, Senna occidentalis, Thevetia ahouai, Tithonia diversifolia* [78, 82, 83, 88, 89].
Lymphoma	*Bursera fagaroides, Camellia sinensis, Gymnosperma glutinosum, Lophophora williamsii, Punica granatum, Trifolium pretense* [78].
Myeloma	*Curcuma longa, Magnolia officinalis* [78, 82].
Nasopharynx	*Acacia pennatula, Acaciella angustissima, Adenophyllum aurantium, Aechmea bracteata, Agave salmiana, Albizia occidentalis, Alnus jorullensis jorullensis, Alvaradoa amorphoides, Amphipterygium adstringens, Annona purpurea, Astianthus viminalis, Bauhinia divaricata, Begonia heracleifolia, Bidens squarrosa, Bonellia macrocarpa pungens, Bromelia pinguin, Bursera bipinnata, B. copallifera, Caesalpinia gaumeri, Casearia nítida, Casimiroa tetrameria, Castela tortuosa, Chrysophyllum mexicanum, Citharexylum ellipticum, Cladocolea grahamii, Cochlospermum vitifolium, Colubrina macrocarpa, Comarostaphylis polifolia, Combretum fruticosum, Crossopetalum gaumeri, Croton reflexifolius, Cuphea aequipetala, Dalea carthagenensis, Dialium guianense, Dioon spinulosum, Diospyros anisandra, D. tetrasperma, Dorstenia contrajerva,D. drakena, Epaltes mexicana, Euphorbia pulcherrima, Galphimia glauca, Gossypium hirsutum, Hamelia patens, Havardia albicans, Heterotheca inuloides, Hintonia latiflora, Hippocratea excelsa, Hyptis suaveolens, Iostephane heterophylla, Ipomoea orizabensis, Ipomoea pauciflora, Jacaranda mimosifolia, Jatropha gaumeri, Krameria pauciflora, Lantana involucrata, L. urticifolia, Leucaena leucocephala, Linum scabrellum, Lobelia laxiflora, Luehea alternifolia, Microgramma nítida, Montanoa leucantha, Morinda royoc, Nernstia mexicana, Pachycereus webery, Pentalinon andrieuxii, Phoradendron carneum, P. galeottii, P. reichenbachianum, Picramnia antidesma, Pinus patula, Piranhea mexicana, Piscidia piscipula, Pithecellobium unguis-cati, Plumbago pulchella, Psidium guajava, P. sartorianum, Psittacanthus calyculatus, Ratibida latipalearis, R. mexicana, Rhizophora mangle, Schkuhria schkuhrioides, Senna racemosa, Solanum chrysotrichum, S. lanceolatum, Stenorrhynchos lanceolatus, Swietenia humilis, S. macrophylla, Tecoma stans, Tradescantia discolor, T. zebrina, Vachellia campechiana, Verbesina persicifolia, Viguiera decurrens, Zea mays* [8].

Table 3 continued..

Neck	*Camellia sinensis* [88].
Neuroblastoma	*Bixa rellana, Capsicum annum, Carica papaya, Larrea tridentata, Smilax aristolochiifolia, Vanilla planifolia, Zea mays* [8, 78].
Osteosarcoma	*Curcuma longa* [78].
Ovary	*Camellia sinensis , Cladocolea grahamii, Galphimia glauca, Ipomoea wolcottiana, Magnolia officinalis, Pentalinon andrieuxii, Persea americana, Phoradendron galeottii, Phoradendron reichenbachianum, Smallanthus rellana, Viburnum jucundum, Viguiera decurrens* [78, 81, 82].
Pancreatic	*Annona purpurea, Curcuma longa, Persea americana* [78].
Prostate	*Amphipterygium adstringens, Annona purpurea, Camellia sinensis, Casearia sylvestris, Cuphea aequipetala, Persea americana, Petiveria alliacea, Psacalium peltatum, Punica granatum, Trifolium pretense, Valeriana sorbifolia* [89].
Rectal	*Curcuma longa* [78].
Skin	*Camellia sinensis, Maytenus chuchuhuasca, Maytenus krukoyii, Maytenus macrocarpa, Trifolium pretense* [78, 83].
Stomach	*Zea mays* [8].

Table 4. Promising candidate drug molecules from plants as potential anti-cancer chemotherapeutic agents.

Compound	**Plant**	**Cancer type**	**Phase clinical**
4-Ipomeanol	*Ipomoeca batatas*	Lung, Hepatocellular carcinoma [6, 90].	I/II
Betulic acid	*Ziziphus mauritiana*	Dysplastic melanocytic nevi [91].	I/II
Combretastatin A4	*Combretum cafrum*	Anaplastic thyroid carcinoma and other cancer [92].	II
Curcumin	*Curcuma longa*	Pancreatic [93].	II
Ellipticine	*Bleekeria vitensis*	Advanced breast [6, 94].	Planned
Epigallocatechin-3-gallate	*Camellia sinensis*	Lung, ovarian skin, prostate, bladder, breast [78].	I/II
Genistein	*Glycine max, Pistacia vera, Trifolium pretense*	Leukemia, breast, prostate [78, 95].	I/II
Homoharringtonine	*Cephalotaxus harringtonia*	CML and solid Tumors [96].	II/III
Indigo, Indirubin, Mesoindigo	*Baphicacanthus cusia, Indigofera tinctoria, Indigofera suffruticosa, Isatis tinctoria, Polygonum tinctorium*	CML [91].	II
Lycopene	*Momordica cochinchinensis*	Prostate [78]	I/II
Perillyl alchol	*Apium graveolens, Lavandula x intermedia, Mentha x piperita, M. spicata*	Metastatic breast cancer refractory [97].	II

Table 4 continued..

Phenoxodiol	*Glycine max*	Chemosensitizer (ovarian cancer), Cervical, prostate [98].	I
Promegrante	*Punica gratum*	Prostate, FL, BPH [78].	II/III
Protopanaxadiol	*Panax ginseng*	Lung, solid tumors, breast, colon-rectum, lung, pancreatic [91].	I Approved
Resveratrol	*Vitis vinifera*	Colon, solid tumors, follicular lymphoma [78].	I/II
Saprothoquinone / Salvicine	*Salvia prionitis*	Solid tumors [99].	II
Silvestrol episilvestrol	*Aglaia foveolata, A. leptantha*	Leukemia [91].	Planned
Triptolide	*Tripterygium wilfordi*	Solid tumors [13].	I

Abbreviations: BPH: Benign prostate hyperplasia, CML: Chronic Myelogenous Leukemia, FL: Follicular lymphoma

identified. The fact that thus far only a relative handful of natural products have been evaluated for their anti-cancer potential holds promise for the identification of agents acting through even more sophisticated mechanisms.

There are an impressive number of higher plant-derived anti-cancer drugs of diverse structural types (Table 4), in both present clinical use and as antineoplastic candidates undergoing clinical trial [11-13]. Another structural type of compounds that represent a promising source of anti-cancer compounds is the xanthones.

Potential anti-cancer activity of xanthones

The xanthones possess a six-carbon conjugated ring structure with multiple double carbon bonds and may be classified into four major groups: simple oxygenated xanthones, xanthone glycosides, prenylated and related xanthones [14]. Over 260 xanthones are currently known to exist in nature [15, 16] and previous studies on different xanthones demonstrated remarkable pharmacological activities including analgesic [17], antioxidant [18], anti-inflammatory [19, 20], anti-cancer [21-24] and antiallergic effects [25], among others.

Xanthones can be obtained from several plant families; the Clusiaceae family, including the genus *Garcinia* and *Calophyllum* are well known as rich sources of bioactive xanthones. *Garcinia* is a large genus of polygamous trees or shrubs, distributed in tropical Asia, Africa, and Polynesia. It consists of 180 species [26] and the most studied species is *Garcinia mangostana.*

G. mangostana or mangosteen, is a tropical tree. Different parts of mangosteen, mostly the pericarp, the leaves, and the bark have been used traditionally for a variety of medical conditions, such as arthritis, diarrhea, dysentery, inflammation, and skin disorders, and have also been utilized for their wound-healing properties. Recently, extracts obtained from the pericarp of mangosteen exhibited a variety of biological properties *in vitro*, such as antioxidant cytotoxic, anti-inflammatory, antibacterial, antifungal, antiviral, and cancer-chemoprevention related effects [27, 28].

Mangosteen is used worldwide as an ingredient of several commercial products including nutritional supplements (Table 5), herbal cosmetics and other pharmaceutical products [29, 30]. The presence of high levels of xanthones in mangosteen fruit rinds (more than 60) were reported by several research groups [14, 31, 32]. The α-mangostin was the first xanthone isolated from *G. mangostana* [33].

Table 5. Dietary supplements with unconfirmed anti-cancer activity.

Herb
Acanthopanax senticosus [100].
Aesculus hippocastanum [101].
Allium sativum [102].
Aloe barbadensis [103].
Andrographis paniculata [104].
Angelia sinensis [105].
Artemisia annua [106].
Asimina triloba [107].
Brassica oleracea L. var. italica Plenck [108].
Bupleurum scorzoneraefolium [85].
Calendula officinalis [109].
Camellia sinensis [110].
Capsicum annuum [111].
Coleus forskohlii [112].
Euterpe oleraceae [113].
Garcinia mangostana L. [114].
Larrea tridentate [115].
Lessertia frutescens [116].
Momordica charantia [117].
Morinda citrifolia [118].
Nerium oleander [119].
Petiveria alliacea L. [120].
Radix isatidis baphicacanthi [121].
Rhamnus purshiana [122].
Sanguinaria canadensis [123].
Sarcandra glabra (Thunb.) Nakai [122].
Scutellaria baicalensis [124].
Symphytum officinale [125].
Triticum aestivum [126].
Uncaria tomentosa [127].
Vaccinium myrtillus [128].
Withania somnífera [129].

The major xanthones obtained from mangosteen are α-mangostin, β-mangostin, γ-mangostin, and methoxy-β-mangostin. The prenyl group is considered to be implicated in the internalization into the cell, which in turn leads to interaction with the signal transduction molecules and the proteins involved in mitochondria permeability transition [21, 34].

The genus *Calophyllum* comprises 180-200 tree species with pantropical distribution [35, 36]. In the American continent, *Calophyllum* genus is represented by 8 species; among them, *C. brasiliense* has the widest distribution from Argentine to Mexico. *C. brasiliense* is used to treat rheumatism, varicose, hemorrhoids, ulcers, inflammation and pain [36, 37]. It is also used as an antimicrobial, cytotoxic, antineoplasic, antispasmodic, antinociceptive, anti-HIV, and antiulcer agent [38-44].

C. brasiliense contains about 20 simple and prenylated xanthones isolated from stem bark and roots. Currently, our research group is evaluating the anti-tumoral potential of prenylated xanthones isolated from heartwood of *C. brasiliense* growing in Mexico [45]. The potential chemopreventive and chemotherapeutic activities of xanthones have been demonstrated in different stages of carcinogenesis (initiation, promotion, and progression) and are known to control cell division and growth, apoptosis, inflammation, and metastasis.

CONCLUSIONS

Multiple lines of evidence from numerous *in vitro* and *in vivo* studies have confirmed that xanthones inhibit proliferation of a wide range of human tumor cell types by modulating various targets and signaling transduction pathways, supporting its remarkable potential as an anti-cancer agent [46].

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