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REVIEW

Nature's treasurer: plants acting on colon cancer

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Nowadays, neoplastic disease, especially colorectal cancer has been emerged as a major challenge for mankind. For treatment of colorectal cancer some drugs available in market (e.g. Capecitabine, Cetuximab, Trinotecan, etc.) and many are under investigation. Tremendous possibilities are reviewed and collected from the herbal source (natural treasure) for the successful management of colorectal cancer. Intensive research had been done worldwide on the plant source that increases possibilities for providing great opportunities to improve the management of the colorectal cancer. Many researchers had concluded that herbal source can be useful for the successful management of colon cancer. This review provides a brief account on various plants that can be used for therapeutic purposes. Author suggests developing a chemical base moiety for clinical researchers to run clinical trials and future research on such capable plants.

Key words: Colon Diseases, Plant acting on colon, Colon cancer

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Key words: Colon Diseases, Plant acting on colon, Colon cancer

One of the most important medicinal aims of this century is the prevention, cure and mitigation of cancer. For the past many decades, there have been extensive efforts to evaluate the chemotherapeutic role of substances present in natural products. Medicinal plants are frequently used by traditional healers to treat a variety of ailments and symptoms including diabetes and cancer. According to the World Health Organization, over 80% of the world's populations rely upon such traditional plant-based systems of medicine to provide them primary healthcare [1]. Dietary intake of phytochemical has been associated with decreased risk of cancer and significant survivability of cancer patients [2]. Over 60% of anticancer drugs available in the market are of natural origin. Natural chemical moieties are lead molecules for many of the drugs that are currently in use [3]. Colon cancer is one of the most common malignancies in many regions of the world and is thought to arise from the accumulation of mutations in a single epithelial cell of the colon and rectum [4]. The complex sequence of events occurring during

initiation, development and propagation of tumours is likely the result of lifelong accumulation of a series of mutations [5]. A number of chemical carcinogens such as 1,2-dimethylhydrazine (DMH), azoxymethane (AOM), 2-amino-3-methyl imidazole (4,5f) quinoline (IQ), 2-amino-1-methyl-6-phenyl-imidazo [4,5-6] pyridine (phIP), methylnitrosurea, N-methyl-N-nitro-N-nitrosoguanidine have been used to induce benign and malignant neoplasm in the colon of the rodents. These agents have provided a reasonably accurate experimental model of human colon cancer [6].

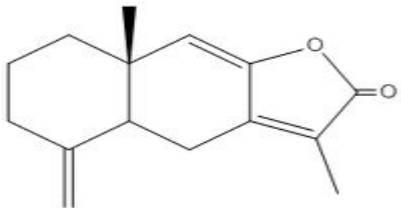
Colorectal cancer:

Large bowel cancer includes cancerous growths in the colon, rectum and appendix. 98% of all cancers in the large intestine are adenocarcinomas. Several studies suggested that the use of aspirin and other NSAIDs have a protective effect against colon cancer. Colorectal cancers arise from adenomatous polyps in the colon. These mushroom-shaped growths are usually benign, but some develop into cancer over time. Localized colon cancer is usually diagnosed through colonoscopy. Invasive cancers that are confined within the wall of the colon (TNM stages I and II) are curable with surgery. If untreated, they spread to regional lymph nodes (stage III), where up to 73% are curable by surgery and chemotherapy. Cancer that metastasizes to distant sites (stage IV) is usually not curable, although chemotherapy can extend survival, and in rare cases, surgery and chemotherapy together have seen patients through to a cure. Radiation is used with rectal cancer [7].

1. **Atractylodes japonica**: It consists of fresh roots or rhizomes of Atractylodes japonica Koidz, family Compositae. The rhizome of Atractylodes japonica Koidz is a perennial plant native to North Asia and has been commonly used for centuries as a therapeutic remedy to treat water retention, arthritis and digestive disorders in Korean traditional medicine [8].

Han Choi et.al., had isolated Atractylodiol (ATD) and diacetyl-atractylodiol (DATD) from the chloroform fractions of Atractylodes japonica and results demonstrated that acetylene compounds, atractylodiol (ATD) and diacetyl-atractylodiol (DATD), are the effective phytochemicals of Atractylodes japonica to stimulate the motility of distal colon in rats, and atractylodiol (ATD) possibly enhanced the spontaneous contractility of distal colon through inhibiting the mechanism of nitrergic–purinergic relaxation [9].

Researchers from China reported that atractylenolide I extracted from large-head atractylodes rhizome could help in management of gastric cancer. They found the chemical helps in alleviating symptoms, in modulating cytokine and in inhibiting PIF proteolysis of gastric cancer cachexia. [10]



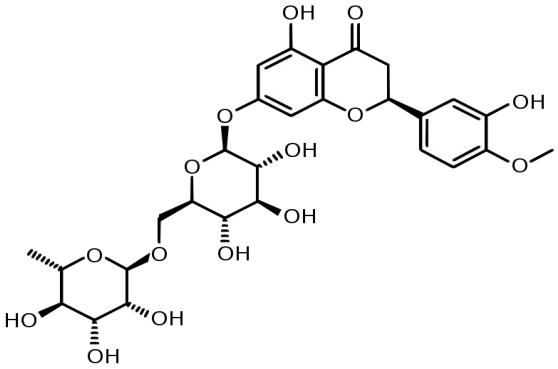
Atractylenolide I

2. **Poncirus trifoliata**: It is a member of the family Rutaceae and is native to northern China and Korea and is also known as the Chinese Bitter Orange [11].

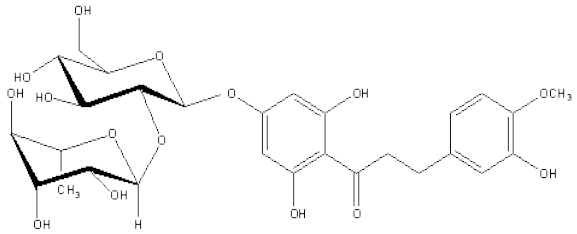
There are many named varieties of Poncirus trifoliata, the most common being Rubidoux, but it is difficult to find any references to precise differences between them. However, it seems clear that there is one group of large-flowered forms and another group with smaller flowers. Additionally,

there is a dwarf form, with twisted stems and curved thorns called 'Flying Dragon' [12].

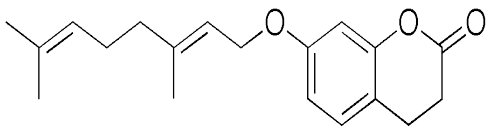
The immature fruits of Poncirus trifoliata (L.) Raf. have been known to reveal a variety of pharmacological properties such as anti-oxidant, anti-platelet, anti-bacterial and antiallergic activities and to contain more than 50 phytochemicals including poncirin, limonene, synephrine, hesperidin, neohesperidin, auraptene and imperatorin [13].



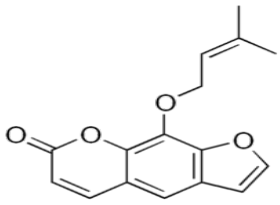
Hesperidin



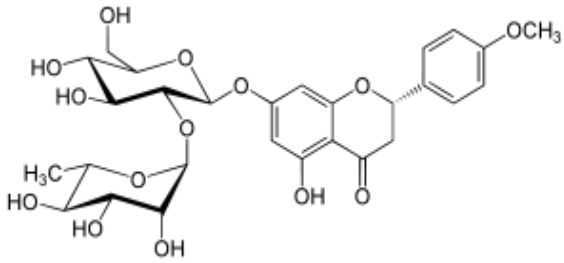
Neohesperidin DC



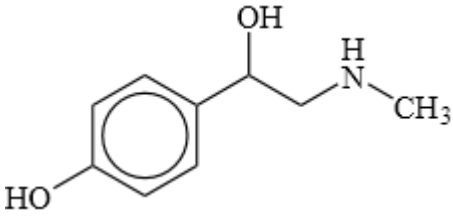
Auraptene



Imperatorin



Poncirin

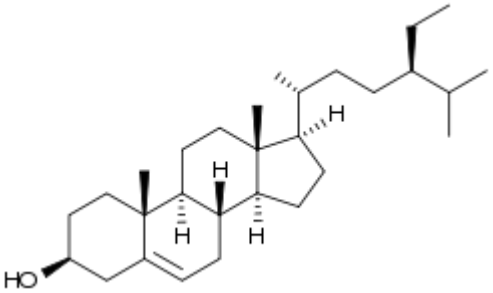


Synephrine

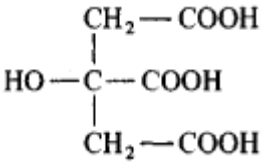
Keun Han Choi et.al., prepared methanolic, n-hexane, chloroform, Ethyl acetate, n-butanol and water extracts of Poncirus trifoliata fruits examined in-vitro and in-vivo on contractility of colonic strips and colonic luminal transit in rats. It was found that only hexane extract of PT (PTHE) dose-dependently increased the low frequency contraction of longitudinal muscle in distal colonic strips [14].

Recently several plant derived natural compounds have been screened for their anticancer activity in order to identify putative compounds with novel structures or mechanism of action. In the present study, fruits of Poncirus trifoliata were extracted with acetone and loaded onto silica gel column. The column was eluted with different solvents to obtain two bioactive compounds. The purity of compounds was analyzed by HPLC and their structures were identified by 1H and 13C NMR experiments as β-sitosterol and 2-hydroxy-1,2,3-propanetricarboxylic acid 2-methyl ester (HPCME). β-Sitosterol, HPCME, and trolox were tested for their antioxidant capacity by oxygen radical absorbance capacity (ORAC) measurement. Further, these compounds were tested for their inhibition of cancer cell proliferation and apoptosis using human

colon cancer cell line (HT-29). These results were compared with the corresponding activity on non-cancerous (COS-1 fibroblast) cells. Cell proliferation and induction of apoptosis were determined by MTT assay and nuclear staining. The MTT assay indicated that both the compounds exhibited differential inhibition at various concentrations. Significant arrest of cell growth was observed with β-sitosterol even at low concentration such as 0.63 μM in 48 h and none of the compounds exerted any apparent cytostatic effects on the non-cancerous COS-1 fibroblast cells. Growth inhibition assay suggested the potential use of bioactive compounds as cancer chemopreventive and therapeutic agents. This is the first report on HPCME isolation and identification from Rutaceae family and β-sitosterol from P. trifoliata. (15)



(β-sitosterol)



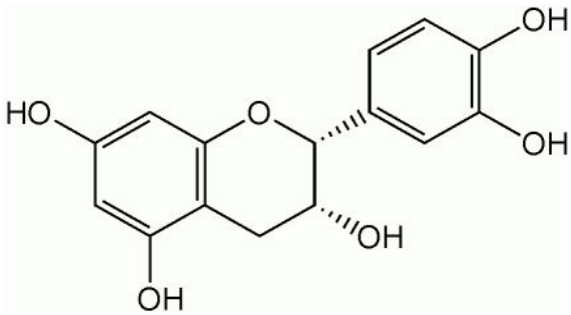
(HPCME)

3. Aronia melanocarpa (Chokeberry): Aronia melanocarpa (chokeberries) are two to three species of deciduous shrubs in the family Rosaceae, native to eastern North America and has been extensively cultivated in Denmark, Eastern Europe and Russia. They are most commonly found in wet woods and swamps. Chokeberries are cultivated as ornamental plants and also because they are very high in antioxidant pigment compounds, like anthocyanins. The name "chokeberry" comes from the astringency of the fruits which are inedible when raw. The berries can be used to make wine, jam, syrup, juice, soft spreads, tea and tinctures. The fruits are eaten by birds (birds do not taste astringency and feed on them readily), which then disperse the seeds in their droppings.

The chokeberries are often mistakenly called chokecherries, which is the common name for Prunus virginiana. Further adding to the ambiguity, there is a cultivar of Prunus virginiana named 'Melanocarpa', easily confused with Aronia melanocarpa. Chokecherries are also high in antioxidant pigment compounds, like anthocyanins, further contributing to confusion. (16)

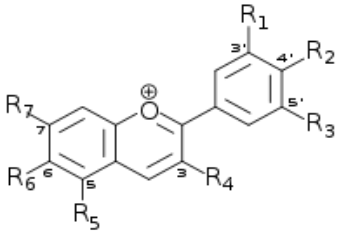
It contain high content of antioxidants and polyphenols mostly anthocyanins and procyanidins.

Maria et.al, suggested that consumption of berries and red fruits rich in polyphenols may contribute to the reduction of colon cancer and investigated the response of subconfluent Caco-2 cells to a subtoxic dose of a chokeberry. It was concluded that exposure of chokeberry juice inhibited Caco-2 cell proliferation by causing G2/M cell cycle arrest [17].



Epicatechin (EC), one of the possible building blocks of proanthocyanidins

There is list of selected anthocyanidins and their substitutions

Anthocyanidin	Basic structure	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Aurantinidin		−H	−OH	−H	−OH	−OH	−OH	−OH
Cyanidin		−OH	−OH	−H	−OH	−OH	−H	−OH
Delphinidin		−OH	−OH	−OH	−OH	−OH	−H	−OH
Europinidin		$-OCH_3$	−OH	−OH	−OH	$-OCH_3$	−H	−OH
Luteolinidin		−OH	−OH	−H	−H	−OH	−H	−OH
Pelargonidin		−H	−OH	−H	−OH	−OH	−H	−OH
Malvidin		$-OCH_3$	−OH	$-OCH_3$	−OH	−OH	−H	−OH
Peonidin		$-OCH_3$	−OH	−H	−OH	−OH	−H	−OH
Petunidin		−OH	−OH	$-OCH_3$	−OH	−OH	−H	−OH
Rosinidin		$-OCH_3$	−OH	−H	−OH	−OH	−H	$-OCH_3$

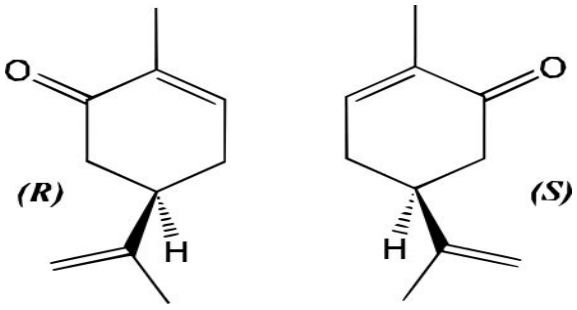
Selected anthocyanidins and their substitutions

4. **Peucedanum japonicum (Japanese common name: botan-bofu)**: The genus Peucedanum is a large group comprising more than 120 species, widely distributed in Southern and Eastern Asia including Japan. Peucedanum longifolium and P. palimbioides are species occurring naturally in Turkey but also in central and Eastern Europe. As with all plants belonging to the Apiaceae family, they are rich in coumarins and essential oils, but also some phenolic acids have been investigated in genus Peucedanum (18)

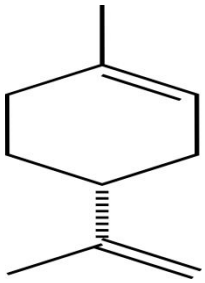
Epidemiological studies have demonstrated that dietary factors play a critical role in the development of human colon cancers [20].

Takamitsu et.al., investigated the modifying effect of dietary Peucedanum japonicum and antioxidant effect on azoxymethane (AOM)-induced rat colon carcinogenesis. Modification of the preneoplastic lesions of both aberrant crypt foci (ACF) and b-catenin accumulated crypts (BCAC) in colon carcinogenesis, microscopically and immunohistochemically was observed and it was suggested that Peucedanum japonicum may have chemopreventive potential for colon carcinogenesis [21].

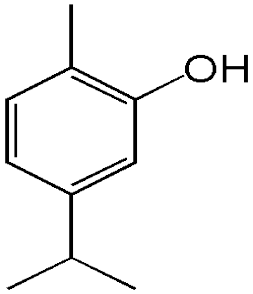
5. **Carum carvi**: Caraway is a shrub with a long history as a medicinal plant since ancient times [17]. Caraway consists of the dried ripe fruits of Carm carvi Linn., family Umbelliferae. It is indigenous to Holland and Central Europe. Main chemical constituents contain 2.5 to 8% volatile oil, about 10% of fixed oil, 15% of proteins and resin. Volatile oil contains 45 to 65% of carvone, limonene, dihydro-carvone and traces of carvacrol.



Carvone



Limonene



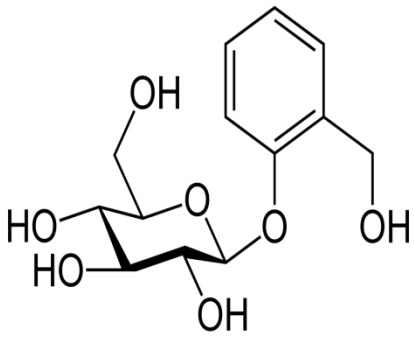
Carvacrol

Muthaiyan et.al., studied and found that the constituents of caraway possess potent chemopreventive properties and can be considered for its possible use as a colon cancer preventive agent. A study was undertaken to determine the effects of desculated doses of caraway against DMH-induced formation of ACF. The levels of fecal bile acids, neutral sterols, and intestinal alkaline phosphatase activities in association with ACF induced by DMH were also examined. Result showed that doses of caraway inhibited tumorigenesis though the effect of the intermediary dose of 60 mg/kg [22].

6. **Willow bark (Salix species)**: Willows, sallows and osiers form the genus Salix, around 400 species of deciduous trees and shrubs, found primarily on moist soils in cold and temperate regions of the Northern Hemisphere. Most species are known as willow, but some narrow-leaved shrub species are called osier, and some broader-leaved species are referred to as sallow (from Old English sealh, related to the Latin word salix, willow). Some willows (particularly arctic and alpine species) are low-growing or creeping shrubs; for example the Dwarf Willow (Salix herbacea) rarely exceeds 6 cm (2 in) in height, though spreading widely across the ground. (23)

Willow bark has been used throughout the world for centuries as an anti-pyretic and analgesic. Its active constituents, salicin, and its derivates were widely used by 19th century physicians to treat rheumatic fever, different kinds of pain, including back pain, toothache, and headache. In the late 19th century, acetylsalicylic acid (ASA) was synthesised based on the chemical structure of the willowbark constituent, the prodrug salicin [24].

Katarina et.al., examined the effects of the main groups of compounds such as salicylalcohol derivates, flavonoids, proanthocyanidins, and salicin isolated from willow bark extract BNO 1455 on proliferation and apoptosis in human colon and cancer cells. It was concluded that willow bark extract BNO 1455 have fraction of inhibit the cell growth and promote apoptosis in human colon and lung cancer cell lines irrespective of their COX-selectivity [25].



Salicin

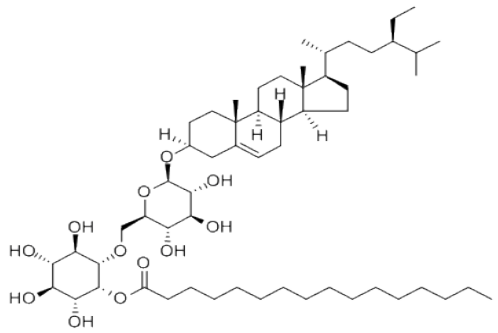
7. **Brassicaceae**: Vegetables of the Brassicaceae family, in particular those of the Brassica genus (broccoli, cabbage, cauliflower, radish, mustard, etc.) have received much attention because they are

reported to have anticancer activity in vitro and in vivo [26].

8. **Withania somnifera**: Withania somnifera, also known as Ashwagandha, Indian ginseng, Winter cherry, Ajagandha, Kanaje Hindi, Amukkara in Tamil and Samm Al Ferakh, is a plant in the Solanaceae or nightshade family. Many closely related species like Withania coagulans (Dunal) – Paneer dodi, Ashutosh booti are morphologically very similar to the species. It grows as a short shrub (35–75 cm) with a central stem from which branch extend radially in a star pattern (stellate) and covered with a dense matte of wooly hairs (tomentose). The flowers are small and green, while the ripe fruit is orange-red and has milk-coagulating properties. The plant also has long brown tuberous roots that are used for medicinal purposes. It is cultivated in many of the drier regions of India such as Manasa, Neemuch and Jawad tehsils of the Mandsaur District of Madhya Pradesh, Punjab, Sind, and Rajasthan. (27)

In Indian traditional medicine, the root extract of W. somnifera was used to treat arthritis, asthma, hypertension, rheumatism [28].

Bolleddula Jayaprakasam et al, extracted various extract from the leaves of Withania somnifera such as sitoindoside IX, 4-(1-hydroxy-2, 2-dimethylcyclpropanone)-2, 3-dihydrowithaferin A, 2, 3-dihydrowithaferin A, 24, 25-dihydro-27-desoxywithaferin A, physagulin D (1-6)-h-D-glucopyranosyl-(1-4)-h-D-glucopyranoside, 27-O-h-D-glucopyranosylphysagulin D, physagulin D, withanoside IV, 27-O-h-D-glucopyranosylviscosalactone B, 4, 16-dihydroxy-5h, 6h-epoxyphysagulin D, viscosalactone B. In vitro studies revealed that Viscosalactone B and 27-O-glucoside derivative may prevent or decrease the growth of tumors in human [29].

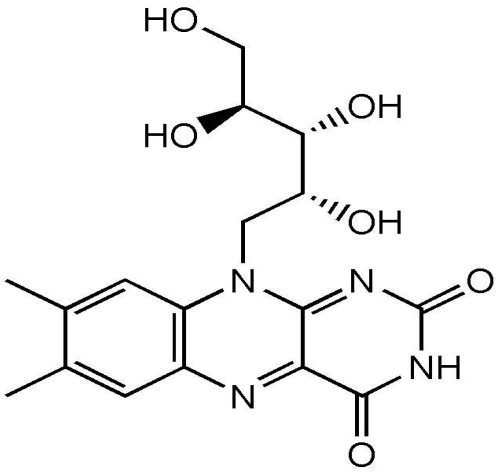


sitoindoside IX

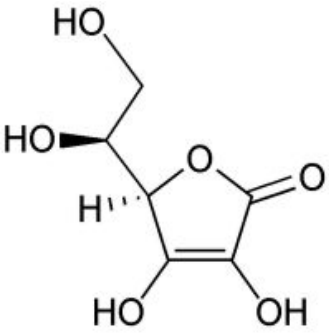
9. **Ilex paraguariensis (Mate tea)**: Mate tea, also known as yerba Mate, is an herbal infusion from the dried leaves of Ilex paraguariensis, belonging to the Aquifoliaceae family. Mate tea contains several classes of chemical constituents mainly caffeoyl derivatives (caffeic acid, chlorogenic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid and 4,5-dicaffeoylquinic acid), amino acids, flavonoids (quercetin, kaempferol and rutin), minerals (P, Fe and Ca), vitamins C, B1 and B2 [30].

Free radicals play a direct role in pathogenesis of several human diseases, such as cancer, rheumatic arthritis and various neurodegenerative and pulmonary diseases [31].

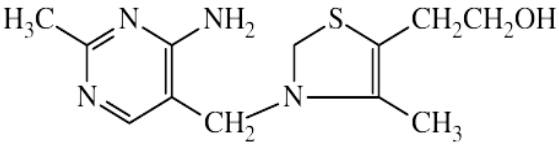
Elvira et.al., experimentally determined that mate tea acted as inhibitor of HT-29 and CaCo-2 cells growth, and deserves further studies to determine efficacy and safety in vivo [32].



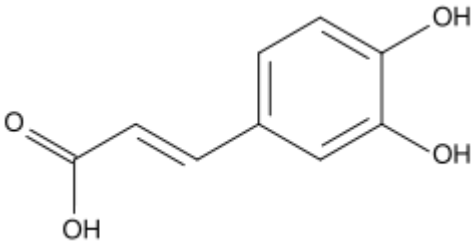
Vitamin B2



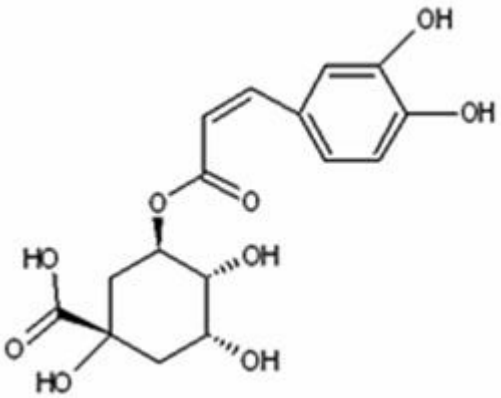
Vitamins C



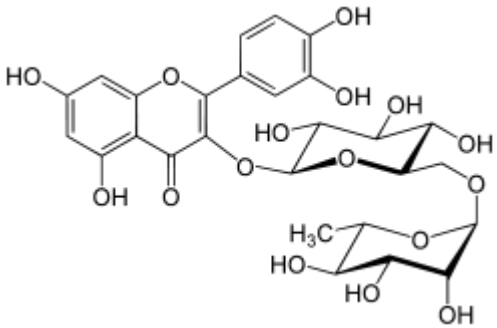
THIAMINE



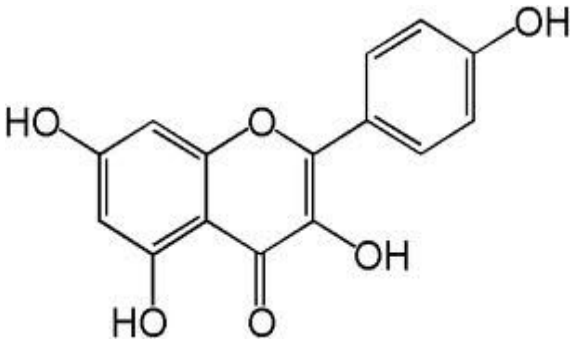
Caffeic Acid



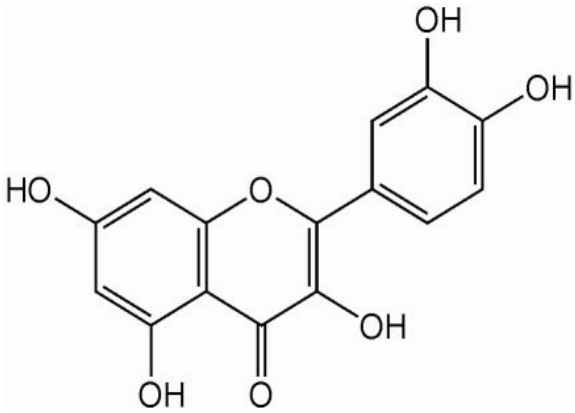
Chlorogenic Acid



Rutin



Kaempferol

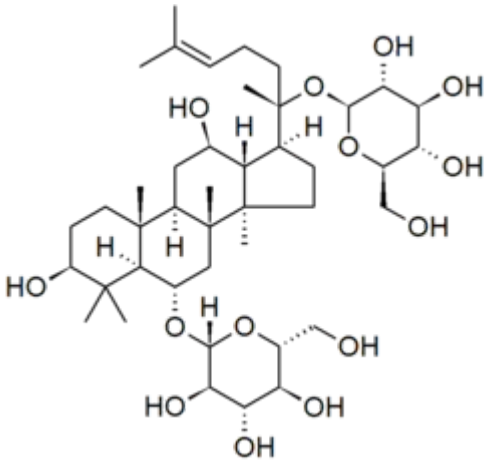


Quercetin

10. Panax quinquefolius: It is most commonly known examples are Xiyangshen, also known as American Ginseng. (33)

M. L. King et al, determined the effects of water extracted ginseng or its ginsenoside and polysaccharide fractions on the proliferation of human colon cancer cells and examined the role of p 21 in mediating these effects using wild type and

p21-/- HCT 116 human colon carcinoma cells and suggested that p 21 functions to arrest HCT 116 wild type cells treated with GE, while p21 deficient cells undergo cell death in a ginseng constituent dependent manner [34].



Ginsenoside A2

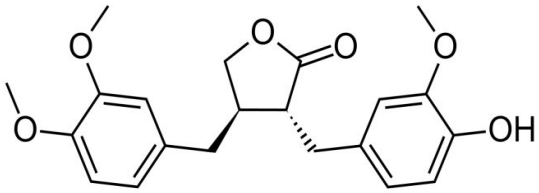
11. **Cynodon dactylon (L.) Pers.**: Cynodondactylon (L.) Pers, root is used as cure for cancer in Indian Traditional medicine [35].

Arul et.al., evaluated the chemopreventive property of Cynodondactylon. The antioxidant, antiproliferative and apoptotic potentials of the plant were investigated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, nitric oxide radicals cavenging activity (NO-) and MTT assay on four cancer cell lines (COLO 320 DM, MCH-7, AGS, A549) and a normal cell line (VERO). In vivo chemopreventive property of the plant extract was studied in DMH-induced colon carcinogenesis. The methanolic extract of C. dactylon was found to be antiproliferative and antioxidative at lower concentrations and induced apoptotic cell death in COLO320DM cells. Treatment with methanolic extract of C. dactylon increased the levels of antioxidant enzymes and reduced the number of dysplastic crypts in DMH-induced colon of albino rats. The investigation revealed the anticancer potential of methanolic extract of C. dactylon in COLO 320 DM cells and experimentally induced colon carcinogenesis in rats [36].

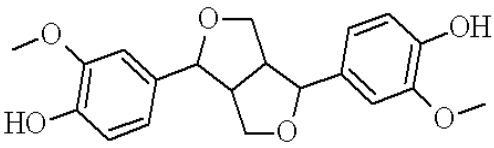
12. **Centaurea montana (Asteraceae)**: Centaurea montana (family: Asteraceae alt. Compositae), an erect plant with large, reddish, blue centre flower heads, is native to Australia, Belgium and Italy [37].

Number of flavonoids, 2–5 acetylenes and a lignan, arctigenin have previously been reported from the aerial parts of C. montana [38].

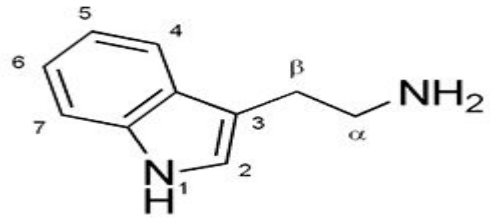
Mohammad et.al., extraced the methanolic extract of the seeds of Centaurea montana, which on RP- HPLC analysis afforded a flavanone, montanoside, six epoxylignans, berchemol, berchemol 40-O-b-D-glucoside, pinoresinol, pinoresinol 4-O-b-D-glucoside, pinoresinol 4,40-di-O-b-D-glucoside, pinoresinol 4-O-apiose-(1/2)-b-D-glucoside, two quinic acid derivatives, trans-3-O-p-coumaroylquinic acid, cis-3-O-p-coumaroylquinic acid, and eight indole alkaloids, tryptamine, N-(4-hydroxycinnamoyl)-5-hydroxytryptamine, cis-N-(4-hydroxycinnamoyl)-5-hydroxytryptamine, centcyamine, cis-centcyamine, moschamine, cis-moschamine and a dimeric indole alkaloid, montamine. Montamine showed significant in vitro anticolon cancer activity [39].



Arctigenin



Pinoresinol

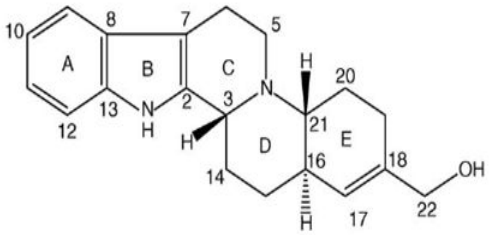


Tryptamine

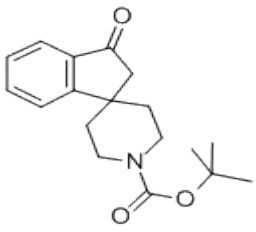
13. **Nitraria tangutorum L**: The Nitraria genus, which belongs to the Zygophyllaceae family, is a kind of shrub that produces esculent berries. (40)

Plants of Nitraria genus are known to contain indoloquinolizidine alkaloids including quinazolines, quinolizidines, and spiropiperdines. A novel b-carboline alkaloid, tangutorine, was isolated from the leaves of Nitraria tangutorum L [41].

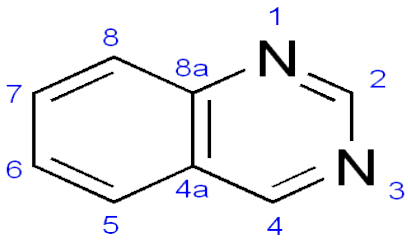
A novel b-carboline alkaloid, tangutorine (benz[f]indolo[2,3-a]quinolizidine) has been isolated from the leaves of Nitraria tangutorum L. The in vitro treatment with low doses of tangutorine slightly stimulated the proliferation of human colon cancer HT29 cells until at concentrations higher than 6.25 mg/ml when the cell numbers, cellular MTT reduction, and cell proliferation by 3H-thymidine incorporation decreased in a dose-dependent manner (IC50 = 15 mg/ml = 48 mM) [42].



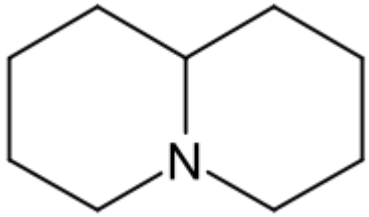
Tangutorine



Spiropiperidine



Quinazolines



Quinolizidine

14. **Pistacia lentiscus L. var. chia**: Pistacia lentiscus is a evergreen shrub or small tree of the Pistacio genus growing up to 4 m (13 ft) tall which is cultivated for its aromatic resin. (43)

The plant Pistacia lentiscus L. var. chia grows particularly and almost exclusively in the South region of Chios Island, Greece and produces a resin, known as Chios mastic gum (CMG).

50% ethanol extract of the plant-derived Chios mastic gum (CMG), contains compounds which inhibit proliferation and induce death of HCT116 human colon cancer cells in-vitro. Study suggested that CMG either induces an anoikis form of cell death in HCT116 colon cancer cells that includes events associated with caspase-dependent pathways or might be developed into a chemotherapeutic agent for the treatment of human colon and other cancers [44].

15. **Coriandrum sativum**: Coriander (Coriandrum sativum) is an annual herb in the family Apiaceae. Coriander is native to southern Europe and North Africa to southwestern Asia. It is a soft, hairless plant growing to 50 centimetres (20 in) tall. The leaves are variable in shape, broadly

lobed at the base of the plant, slender and feathery higher on the flowering stems. The flowers are borne in small umbels, white or very pale pink, asymmetrical, with the petals pointing away from the center of the umbel longer (5–6 mm) than those pointing towards it (only 1–3 mm long). The fruit is a globular dry schizocarp 3–5 mm diameter. In American culinary usage, the fruits ("seeds") are generally referred to as coriander, the leaves as cilantro. **(45)**

Chithra et.al., studied the biochemical effect of coriander seeds on lipid parameters in 1,2-dimethyl hydrazine (DMH) induced colon cancer in rats. The study showed that the concentrations of cholesterol and cholesterol to phospholipid ratio decreased while the level of phospholipid increased significantly in the DMH control group compared to the spice administered group. Fecal dry weight, fecal neutral sterols and bile acids showed a sharp increase in the coriander-fed group compared with the DMH administered group. Thus, coriander plays a protective role against the deleterious effects in lipid metabolism in experimental colon cancer [46].

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