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A Review

The biological role of bioactive compounds from plants, bacteria, and bee-products in cancer prevention and therapy

Anita Rana[1], Harjit Kaur Bajwa[2]* & Hina Khan[3]

[1]UIBT-Biosciences, Chandigarh University, Mohali-140 413, Punjab, India

[2]Botany Department, Punjab University, Chandigarh-160 014, India

[3]Department of Botany & Environmental Science, SGGSW University, Fatehgarh Sahib-140 407, Punjab, India

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According to World Health Organization about one in six deaths is due to cancer and more or less one third of deaths from cancer are due to obesity and low consumption of vegetables and fruits. Plant-based food may help to lower the risk of cancer since they are the natural sources of nutrients and health enhancing biologically active compounds. Beside plants, food items from animals like milk, meat, egg, honey and other bee-products also have the potential to hamper tumor cell growth and metastasis due to the presence of bioactive compounds. This paper discusses about the consumption of natural food products for cancer prevention since they are an excellent source of secondary metabolites. Prevention is the most economically extended strategy for the control of cancer by making the people aware and providing them with the information they need to adopt healthy lifestyle. The natural food sources possess multiple secondary metabolites that have exhibited anticancer properties by modulating metabolic processes in the body, which results in improving well-being. Even though, the evidence is insufficient, yet modern research recommends natural food to reduce the risk of cancer. Phytochemicals in the food work synergistically in lowering cancer risk. Some help to regulate hormones and other slow cancer cell growth. The potential health benefiting properties of secondary metabolites may call for development of these health-promoting compounds into future therapeutic agents.

Keywords: Anticancer, Bacteria, Bioactive compounds, Flavonoids, Honeybee products, Plants, Polyphenols

Introduction

Cancer is a grave health issue globally and the burden of this disease is accelerating worldwide, exerting immense physical, emotional and financial burden on individuals, families, communities and health system. In 2018, around 9.6 million humans died from cancer and by 2040 this figure will nearly double, with the highest rise in low and middle income countries[1]. Research indicates that 30% of all cancer cases are linked to poor diet. Diet is considered as the most important factor related to human morbidity and mortality. Healthy diet is one of the keys to a healthy life because diet can have a powerful impact on our health. Diet full of vegetables and fruits can lower the likelihood for a variety of common cancers since fruits and vegetables provide a large number of nutrients and health-enhancing phytochemicals such as phenolics, flavonoids, sulphur compounds, anthocyanidines, phytosterols and more. Silymarin, diallyl sulfide, polyphenols, genistein, apigenin, gingerol, curcumin, rosmarinic acid resveratrol, isothiocyanates, sulforaphane, lycopene, are the bioactive compounds with noteworthy anticancer potential. Block *et al* investigated around 200 studies and examined the connection between vegetables and fruits consumption and cancers of the ovary, stomach, oral cavity, pancreas, lung, colon, breast, cervix, esophagus, and found that persons with less fruit and vegetables consumption encounter about twice the risk of tumors as compared to person with lofty consumption[2]. Beside plants some animals especially honey bees modify plant parts such as pollens into even healthier products including pollen, propolis, honey etc. Being rich in bioactive compounds, these bee-products are likely involved as shielding agents for several chronic diseases and also prevent age-related macular degeneration.

Cancer can start in any part of the body when cells grow obdurately and go outside their limits to conquer adjoining organs of the body[1]. There are many types of cancer therapies such as radiation therapy, chemotherapy and immunotherapy however number

*Correspondence:
Phone: +91-9877342893 (Mob)
E-mail: harjitkaurbajwa@gmail.com

of problems occurs when treatment affects healthy tissues or organs. Anticancer therapy using bioactive compounds begins with the testing of material for potential anticancer activity followed by purification of biologically active compounds and testing for *in vitro* and *in vivo* effects. Bioactive components are able to pause, postpone and reverse carcinogenesis by different mechanisms. Cancer is largely an avoidable disease and at least 30-50% of all cancer cases can be prevented by means of food and lifestyle changes. Prevention is the most economical long-term approach for the control of cancer by making people aware and providing them with the information they need to adopt healthy lifestyle. The potential health benefiting properties of bioactive compounds may call for development of these compounds into future therapeutic agent[3]. The aim of this review was to discuss briefly about biologically active components along with their sources that have exhibited anticancer properties and their potential effects in cancer prevention and therapy after dietary consumption.

Relationship between diet and cancer

Cancer has increasingly been identified as a life-style disease and the second leading cause of death worldwide. Researchers from Harvard Medical School discovered that men could lessen the occurrence of bladder cancer, prostate cancer, and kidney cancer by 62%, 40% and 36% respectively by following healthy life-style habit. World Health Organization indicates that, cancer rates in India are substantially lower than more developed countries like U.S. Indian diet which is based on a blend of religious and secular beliefs might be responsible for lowering the rate of this deadly disease[1]. From ancient times, herbs have been important ingredients of traditional Indian food. Ayurveda advised more than 700 plant-based remedies that contain spices and food additives to inspire good health. Several researchers have examined Amrita Bindu, chilies, cumin, kalakhar and various other plants for their apparent cancer preventive qualities. Turmeric, garlic, ginger, cloves, mustard, saffron and cardamom are the other vital ingredients used in Indian cooking. These ingredients not only add taste and flavor to Indian food but also provide numerous biologically active compounds which can act on several potential targets in the pathophysiology of cancer[4]. Actually diet rich in vegetables, fruits, spices and whole grains are practically a mixture of a large number of active phytochemicals (alkaloids, terpenoids, flavonoids, phenolic acids, saponins, tannins, phytosterols) and vitamins and minerals that act synergistically and easily assimilated by human body and help protect against cancer directly through specific anti-carcinogenic compounds and indirectly by maintaining a healthy body weight. Education and awareness regarding the advantageous effects of eating healthy food including fresh fruits and vegetables, whole grains and spices are required to prevent cancer as they play vital role in prevention of diet related diseases.

Plant-based food constitutes the core of day-to-day diet for most of the animals including human beings. There are certain animals such as worker honey bees not only consume plant-based food but also engineered it into healthier products, thus this property makes honey bees the master chemists and chemical engineers in animal kingdom. The success of bees is largely because of this chemistry and therapeutic use of their products viz. pollen, propolis, honey, bee venom, beeswax and royal jelly. Three of these products (venom, royal jelly and beeswax) are chemically synthesized by the bees themselves. The other three (pollen, propolis and honey) are derived from plants and are modified and engineered by the bees for their own use. Because of this property they are regarded as big money makers for the agriculturist; as they collect these substances from plants, add their own secretions, process them in the hive and finally allow them to ripen. These ripened substances serve as commercial bee hive products. The bioactive compounds obtained from these natural products have been found to have therapeutic potentialities against some type of cancers[5].

The bioactive compounds in bee-products responsible for anticancer activities are peptide, monounsaturated and polyunsaturated fatty acids, anethole, flavonoids and polyphenols (bee pollen and bee bread: pinocembrin, diterpenes, triterpenes, chrysin, galangin, coumaric acid, ferulic acid, 3-O-methyl quercetin, caffeic acid and CAPE; propolis: chlorogenic acid, gallicacid, syringeacid, caffeic acid, *p*-coumaricacid, catechin, ferulic acid, chrysin 3–2′-pyrrilonidinyl-kynurenic acid, quercetin; honey: 10-hydroxy-2-decenoic acid; Royal jelly: mellitin; bee venom: phospholipase A_2). Though boundless geographical distribution makes their isolation/extraction, standardization and characterization difficult, still some of them like

phenethyl ester (CAPE), caffeic acid and artepillin C in propolis; methylglyoxal and phenolics in honey; jelleins, royalisin peptides and hydroxy-decanoic acid derivatives in royal jelly, melittin, apamine and allergic phospholipase A2 in bee venom have been identified and isolated[5].

Anticancer activity of bioactive compounds from plants

Biologically active components are extra-nutritional compounds that generally present in small amount in foods. In plants, they are produced by plant cells through metabolic pathways derived from primary metabolism. Plant metabolism comprises a series of complex chemical events of photosynthesis, respiration and the synthesis and degradation of various organic compounds. Carbohydrates, amino acids, proteins, nucleic acids and lipids are the outcomes of primary metabolism and essential for the survival of plants while, the products of secondary metabolism aid in plants growth and development but are not required for the survival of plants (Fig. 1).

The secondary metabolites like phenolics, alkaloids, saponins, flavonoids, terpenoids, tannins, steroids, glycosides, volatile oils, and more are significantly important as medicines, cosmetics, and food additives[6]. They also provide defense to the plants, for example, terpenoids inhibit competing plants; flavonoids provide protection against free radicals produced during photosynthesis and alkaloids protect from herbivores or insects. The continued use of plants as food and medicine depends on the knowledge of pharmaceutically important compounds present in plants. Approximately 35,000-70,000 plants species have been screened for their pharmacological uses. There are many classes of natural compounds from different plants that have shown anti-carcinogenic properties (Table 1). Polyphenols are the widely distributed and most studied group of bioactive compounds in plants and display many anti-carcinogenic properties. The anticancer ability of polyphenols has mainly been credited to their potent antioxidant and anti-inflammatory activities.

The fruits like strawberries and raspberries strongly inhibited esophageal cancer in animals due to the presence of phenols such as ellagic acid[7]. Similarly, catechins and related compounds present in green tea are the most potent anti-carcinogenic antioxidants and are active in all phases of carcinogenesis. Green tea polyphenols are highly effective against skin cancer. Likewise, the leaves of *Murraya koenigii* are rich source of phenolic compounds (Fig. 2). Ghasemzadeh *et al* investigated the total phenolic content and anti-carcinogenic properties of leaves of *Murraya koenigii* collected from Johor, Kelantan and Selangor in Malaysia and found that leaf extract from all the locations revealed significant anti-carcinogenic

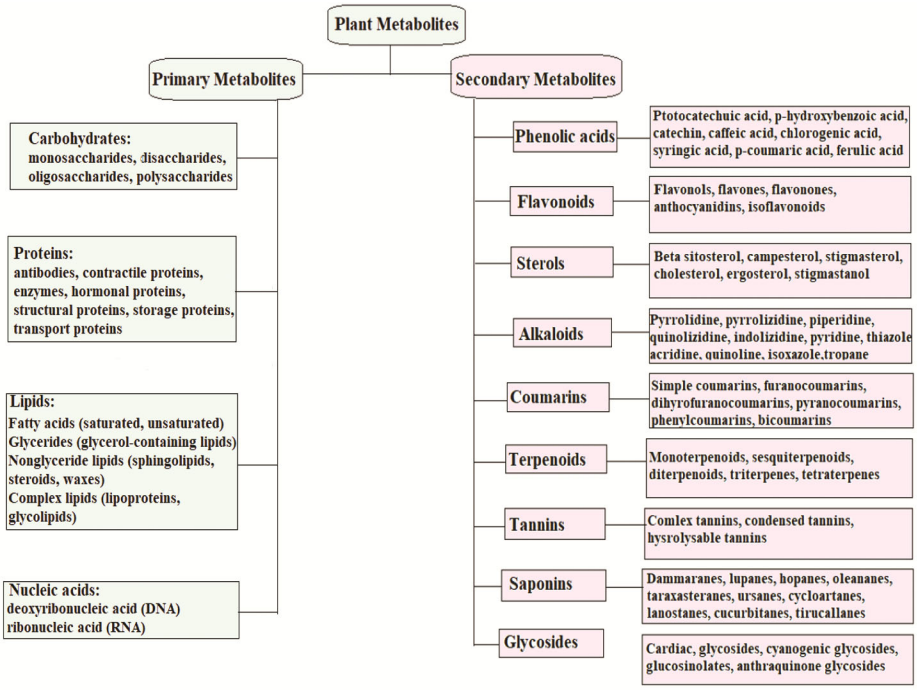

Fig. 1 — Bioactive compounds from plants' primary and secondary metabolisms

Table 1 — Bioactive compounds from plants and their targets with anti-cancer activities

Bioactive compounds	Target cancer	Biological activity	Source	Reference
Ellagic acid	Esophageal	Anticancer	Strawberries and raspberries	[7]
Polyphenols	Skin	Anticancer	*Murraya koenigii*	[8]
Anthocyanin	Lung	Anticancer	*Vitis coignetiae*	[26]
β-sitosterol	Colorectal	Anticancer	*Neochloris oleoabundans*	[40]
Glucosinolates, indoles and isothiocyanates	Lung, colorectal	Anticancer	Broccoli, cauliflower, cabbage	[40]
Indole-3-carbinol	Prostate	Anticancer	-	[11]
Phloretin	Colon	Anti-proliferative, apoptosis	*Malus domestica*	[19]
Carotenoids	Colorectal	Anti-proliferative		[19]
Catechins	Skin	Anticancer	Green tea	[41]
Punicalagin	Breast	Anticancer	*Pomegranate*	[9]
Curcumin	Breast	Apoptosis	Curcumin nanocochleates	[20]
Garcinol, curcumin	Pancreatic	Anticancer	*Garcinia indica*, *Curcuma longa*	[42]
Phloretin	Lung	Anti-proliferative, apoptosis	*Malus domestica*	[19]
Phenols and flavonoids	Breast	Anticancer	*Phyllostachys edulis*	[15]
Papain, lycopene, betacarotinoid, benzylisothyocynate, betacryptoxanthin, benzylglucosinolate, caffeic acid, chlorogenic acid, protocatachuic acid and quercetin	Breast, liver, colon, ovarian, uterine	Anticancer	*Carica papaya*	[16]
β-sitosterol and 2-hydroxy-1, 2, 3-propanetricarboxylic acid 2-methyl ester	Colon	Anticancer	*Poncirus trifoliate*	[17]
Curcumin, demethoxycurcumin, and bisdemethoxycurcumin	Variety of tumor cells	Anticancer	Turmeric	[20]
Terpenoids, phenolic compounds	Breast	Anticancer	*Avicennia alba*	[24]
piperine, piperlongumine, guineensine, chabamide, pellitorine	Malignant and non-malignant	Apoptosis	*Piper* sp.	[26]
Anthraquinones emodin and aloe-emodin	Breast	Anticancer	*Rheum palmatum*	[28]

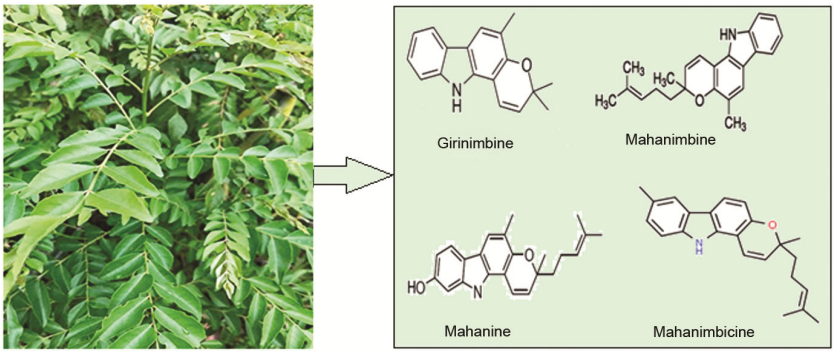

Fig. 2 — Representative images of *Murraya koenigii* and chemical structures of some selected bioactive compounds in leaves of *Murraya koenigii*

abilities and inhibited the growth of breast cancer cell line (MDA-MB-231)[8]. It has also been found that, highest suppression of MDA-MB-231 cell was caused by the leaf extract of *Murraya koenigii* from Kelantan. This activity is probably due to high concentration of total phenols (3.771 and 14.371 mg g^{-1} DW) in the leaf extract from Kelantan location, followed by Selangor (3.146 and 12.272 mg g^{-1} DW) and Johor (2.801 and 12.02 mg g^{-1} DW), respectively[8]. The *Murraya koenigii* leaf extract from Kelantan also showed highest concentration of gallic acid (0.933 mg g^{-1} DW) followed by Selangor (0.904 mg g^{-1} DW) and Johor (0.813 mg g^{-1} DW) location[8].

Punicalagin, a polyphenol from pomegranate possesses potential anti-carcinogenic properties however; it is not absorbed in its intact form but hydrolyzed to ellagic acid moieties and metabolized into short lived metabolites of ellagic acid. Shirode *et al* evolved a new articulation of pomegranate polyphenols (poly (D,L-lactic-*co*-glycolic acid)–poly(ethylene glycol) and evaluated its anticancer activity in MCF-7and Hs578T breast cancer cell. Confocal fluorescent microscopy revealed that this compound was efficiently taken up within 24 hours and showed a 2 to 12 fold intensified effect on the inhibition of cell growth as compared to their free counterparts[9].

There are mainly two mechanisms by which polyphenols prevent cancer; one is blockage of reactive constituents from DNA and stimulation and detoxification of oncogenic elements while the second mechanism works through modulation of carcinogen metabolism. In the first mechanism, food components may interfere with the proliferation of altered cells in such a way that further growth is impeded.

Besides phenolic compounds, vegetables and fruits are also rich in dietary fibre and play a key role in weight management as obesity is a powerful risk factor for cancer of kidney, breast, pancreas, and oesophagus, etc. The pathogenesis of obesity is related to chronic continuous low-grade inflammation. In obese individual, macrophages are accumulated remarkably in the visceral cells, which raises the levels of pro-inflammatory cytokines, *viz*., tumour necrosis factor alpha (TNF-α), monocyte chemo-attractant protein-1 (MCP-1), interleukin (IL)-1 and IL-6 in their blood. Pro-inflammatory adipokines are connected to aberrant metabolism causing damage to pancreatic β cells, insulin resistance, and glucose intolerance[10]. Dietary intervention with functional food ingredients to promote systemic anti-inflammatory properties of the intestine is one of the most successful strategies to improve obesity by reducing dysbiosis of the gut microbiota.

Cruciferous vegetables like broccoli, cauliflower and cabbage have been enormously studied for their anti-inflammatory and anticancer activities. Crucifers are rich in glucosinolates, indoles and isothiocyanates (Fig. 3), and high intake of cruciferous vegetables has been associated with lower risk of cancer in general, and lung and colorectal cancers in particular. Indole-3-carbinol can inhibit the growth of prostate cancer by activating a specific gene that encodes phosphate and tensin homolog (PTEN). PTEN is a tumor suppressive phosphatase that is active in its dimer configuration. An enzyme, ubiquitin E3 ligase WWP1 encoded by the gene WWP1 suppressed the function of PTEN, dimerization and membrane recruitment[11].

Cucumis sativus, a popular Indian vegetable belongs to the Cucurbitaceae family (Fig. 4), is a rich source of phenolic compounds such as Quercetin 3-L-rhamnoside, Naringenin7-O-β-D-glucoside, Apigenin7-rutinoside, Kaempferol 3-O-sambubioside, Kaempferol-3,7-O-α-L-dirhamnoside, Vicenin 2, Diosmetin-apiosylglucoside, a flavanosideI, Luteolin-6-C-(6-malonyl)hexoside-8-C-pentoside, Lariciresinol 9-O-β-D-glucopyranoside, Luteolin 7-O-glucuronide and Isorhamnetol3-O-rutinoside[12]. It is a common ingredient of salads. *Cucumis sativus* extract has potential antioxidant,

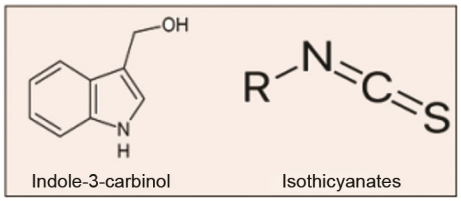

Fig. 3 — Chemical structure of Indole-3-carbinol and Isothiocynates

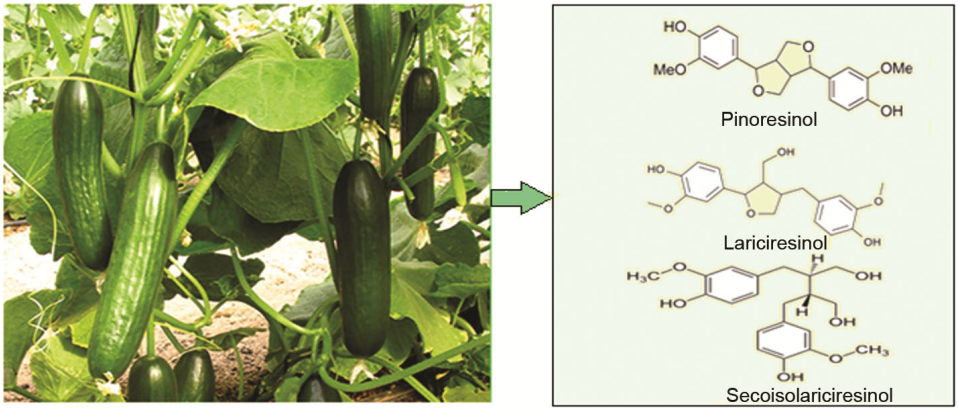

Fig. 4 — Representative images of *Cucumis sativus* and chemical structures of bioactive compounds identified in *Cucumis sativus*

anti-diabetic and lipid lowering activity. Tuama and Mohammed evaluated the anticancer activity of methanol extract of *Cucumis sativus*[12]. Results showed that extract is rich in bioactive compounds and shown anticancer activity with cell lines of (IC_{50}) with MCF 715.6 ± 1.3 and HeLa 28.2 ± 1.

Bamboo shoot, an important source of food for Asian countries contains a plethora of bioactive compounds and possesses a large number of biological activities including anti-oxidants, anti-inflammatory, anti-ulcer, serum cholesterol lowering, and anti-cancer. Bamboo shoot is an excellent source of dietary fibre; nutrient detergent fibre (NDF) (hemicellulose, cellulose, lignin) and acid detergent fibre (ADF) (cellulose, lignin). Research studies indicated that cellulose content in shoots prevents intestine cancer as it promotes the gut microbial flora and peristalsis of intestine. Phenols, phytosterols (Fig. 5) and polysaccharides in bamboo shoots are responsible for anti-inflammatory, anti-oxidants, anti-bacterial, anti-ulcer, and anti-cancer properties of shoots[6]. Ferulic acid, p-coumaric acid, caffeic acid, protocatechuic acid, p-hydroxybenzoic acid, catechin, syringic acid and chlorogenic acid are the major phenolic compounds identified in bamboo shoots using different techniques[6].

It is well documented that bamboo shoot polysaccharides play a key role in weight management. Prevention of high fat diet induced obesity in C57BL/6 mice by administration of 400 mg/kg b.w. of bamboo shoot polysaccharideis reported[13]. This prevention of obesity was proven by reduction in size and weight of adipose tissue, reduction of fat accumulation in liver[13]. Supplementations of bamboo shoot polysaccharide also reduce the production of pro-inflammatory cytokines. Moreover, the enhancement of *Enterobacter* and *Desulfo vibrio* in high fat diet

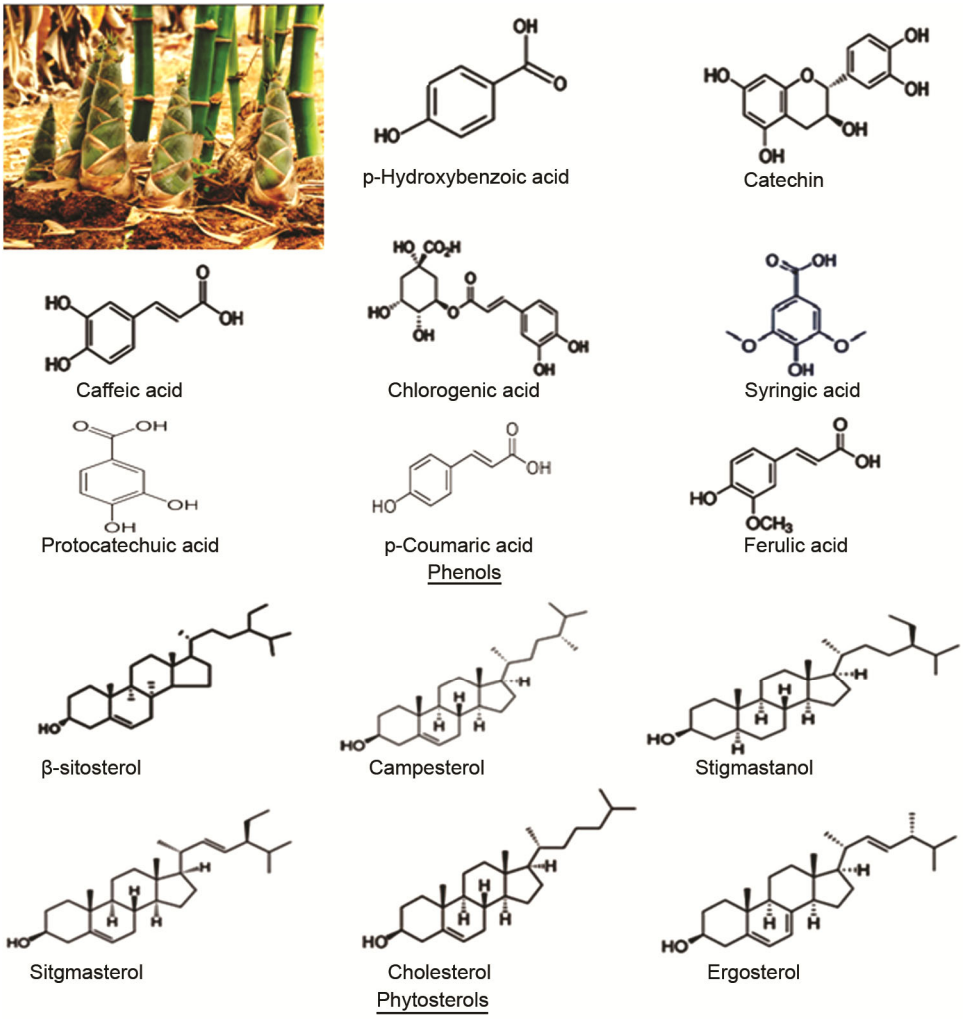

Fig. 5 — Representative image of bamboo shoots, and chemical structures of phenols and phytosterols identified in bamboo shoots

induced obese mice was reverted in bamboo shoot polysaccharide treated groups. When obese mice were treated with ethanolic extract of Sasa *borealis* leaf, reduction in the level of pro-inflammatory cytokines TNF-α, IL-6 was observed[14].

β-sitosterol, campesterol, and stigmasterol are the major sterols identified in bamboo shoots; which are well known for their LDL cholesterol lowering activities and also promote apoptosis in cancer cells. Lin *et al* investigated the anticancer effect of an extract from bamboo *Phyllostachys edulis* on the development of 7,12-dimethylbenz[a] anthracene (DMBA)-induced breast cancer in female Sprague-Dawley rats[15]. They found that bamboo extract delayed the onset of mammary tumor by one week and decreased the tumor incidence by 44% and tumor multiplicity by 67%.

Research consistently shows that high intake of fruits is linked with a lower risk of cardiovascular disease and cancer as fruits are naturally low in calories, fat and sodium. *Carica papaya*, an important medicinal food of tropical and subtropical countries is widely used to treat a range of diseases including cancer. The major phytochemicals present in *Carica papaya* (Fig. 6) are beta-carotinoid, beta-crypto xanthin, lycopene, benzyl glucosinolate, benzyl iso-thyocynate, chlorogenic acid, proto-catachuic acid, caffeic acid and quercetin[16]. An enzyme papain is a major constituent of papaya which is very effective against cancer. It acts on peptide bond and cleaves it involving basic amino acids like phenylalanine, arginine and lysine. Some *in vitro* studies have also been done for testing the cytotoxic effect of *C. papaya* extract against various cancer cell lines such as; colon cancer cell line (DLD-1), hepato-cellular carcinoma cell lines (HepG2 and Huh-7), liver cancer cell line (Hep G2), breast cancer cell line (MDAMB-231, MCF-7 and T47D), uterine cancer cell line (Hela), ovarian cancer cell line (Dov-13), T-cell leukemia cell line (CD26) and acute pro-myelocytic leukemia HL-60 cells[16].

Similarly, fruits of *Poncirus trifoliate* are a rich source of some bioactive compounds such as; 2-hydroxy-1, 2, 3-propane tricarboxylic acid 2-methyl ester and β-sitosterol. These bioconstituents have been tested for seeing apoptosis/necrosis and cancer cell proliferation inhibition by using colon cancer cell line (HT-29) in humans. Their antioxidant potentialities have also been tested by measurement of oxygen radical absorbance capacity. The observations revealed that β-sitosterol is capable of arresting cell cycle/ cell growth even at very low concentration in just two days; hence authenticate the anti-cancerous properties of fruits of *Poncirus trifoliate*[17].

The fruit of Cornus mas (cherry) comprises wide range of phenolic compounds and vitamins. It is a rich source of anthocyanins which makes it suitable for pharmacological and therapeutic properties and hence received serious attention from researchers and scientists all over the world. Radbeh *et al* studied the bioactive compounds of *Cornus mas* extract (CME) for its antioxidant capacity and method of release in semi-digestive conditions by using encapsulated/enteric coated nano-carriers[18]. For determining the effect of encapsulation on the stability of antioxidants, two different forms of CME have been used, one is encapsulated into enteric coated nanocarriers (CME-NCs) and other one is free CME. Their effect was studied on cell viability/cell cycle and apoptosis of tumorogenic cells and results obtained revealed that, nano-encapulation (CME-NCs) as compared to free CME could improve IC_{50} value and it can be responsible for cell cycle arrest at growth phase (G1) and hence apoptosis of tumorigenic cell lines (HT-29)[18].

Malus domestica (apple) is a rich source of polyphenols, which makes it capable of arresting cell

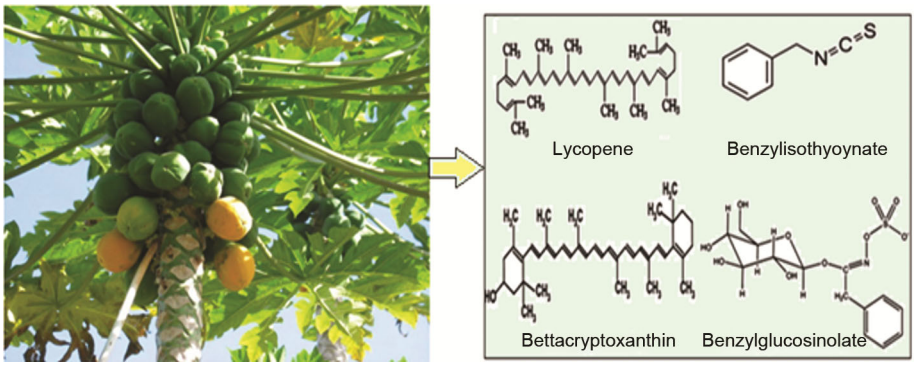

Fig. 6 — Representative image of *Carica papaya,* and chemical structures of bioactive compounds identified in *Carica papaya*

cycle/cell survival/cell growth and proliferation inhibition, hence affecting the cell signaling pathways. It comprises one very important biologically active compound called, Phloretin (Fig. 7) which has the potentiality to inhibit cell proliferation and can induce cell death in lung cancer cell lines and can also potentiates "paclitaxel"-induced DNA laddering formation in liver cell lines of human (Hep G2). It has been corroborated from earlier *in vitro* and *in vivo* studies that Phloretin is an inhibitor of GLUT2 and hence responsible for inhibition of migration/invasion and proliferation of colon cell lines (COLO 205)[19].

Similarly, it's a well-known saying that the heartbeats of Indian food/kitchens are spices. Its unique color, great taste, finger licking flavor and delicious aroma makes it popular worldwide and the reason behind is its richness in spices used while preparing food. Spices not only enhance the taste of food but also have curative properties and used to cure ailments just like natural medicinal plants. One such example is *Curcuma longa* (turmeric), which is well known and found in every Indian kitchen. The major compounds responsible for its therapeutic properties are Curcumin, Demethoxy curcumin and Bis-demethoxy curcumin. Among them, Curcumin (diferuloylmethane) (Fig. 8) is the main curcuminoids responsible for its therapeutic properties as well as for imparting yellow coloration to it. Turmeric comprises anti-cancerous bioactive compounds such as; curcumin, which is responsible for cancer prevention as well treatment. It has unique property of down regulating expression of a number of genes such as; Cyclooxygenase 2 (COX2), nuclear factor (NF)-kappa B, lysyl oxidase (LOX), tumor necrosis factor (TNF), matrix metallopeptidase 9 (MMP-9), nitric oxide synthase (NOS), epidermal growth receptor 1 (EGR-1) and expression of Activator Protein 1 (AP-1) which makes it potential anti-cancerous compound. It also inhibits the expression of kinases (tyrosine kinases and serine/threonine kinases) and the activity of C-Jun N terminal kinase[20].

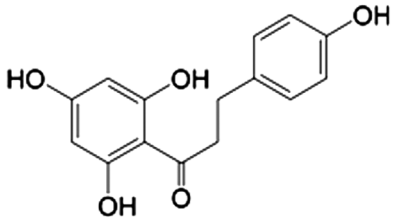

Fig. 7 — Chemical structure of Phloretin

Allium sativum, universally consumed spice and an indispensable ingredient of Indian food is an excellent source of bioactive compounds such as allicin, alliin, diallyl sulfide, aioene and S-allyl-cysteine (Fig. 9).

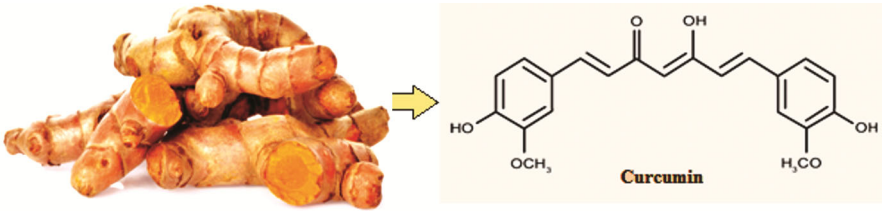

Fig. 8 — Representative image of curcumin, and chemical structure of curcumin

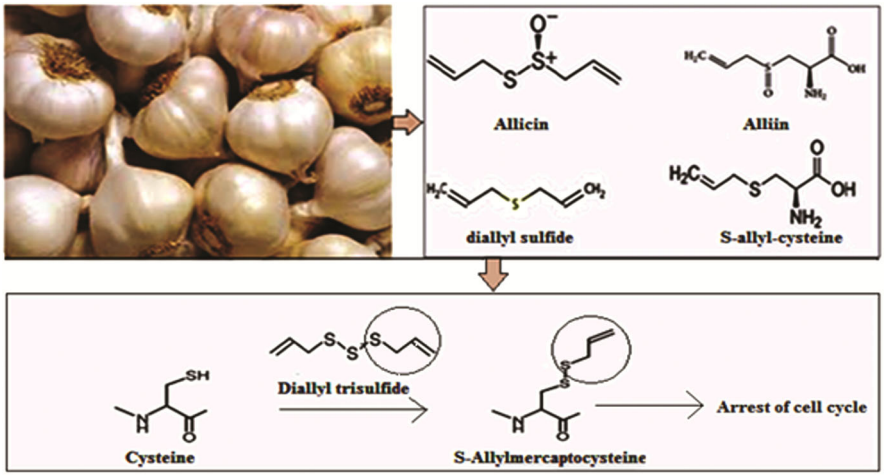

Fig 9 — Representative image of *Allium sativum*, and active constituents in *Allium sativum* and its mechanism of action

These compounds are reported to exhibit anticancer effect through their anti-mutagenic, anti-carcinogenic and antitumor properties[21]. The major bioactive compound di-allyl trisulfide on binding with cysteine residues in beta tubulin forms S allyl-mercaptocystein via caspase-3 activation which is responsible for arresting cell cycle and apoptosis[21].

Tripterygium wilfordii, a Chinese herb commonly called the thunder god vine is a rich source of triptolide, celastrol and tripchlorolide (Fig. 10). These compounds are responsible for modulating the transcriptional activity of signaling molecules such as; NF-κB and hence conferring the anti-cancerous and immunosuppressive activities, and hence can be used as/ emerged as promising drug candidates[22]. Atun and Arianingrum conducted a study on *Kaempferia rotunda's rhizome* against its anti-cancerous activities[23]. This plant is native to Indian subcontinent as well as China and belongs to ginger family. For carrying out its anti-cancerous activities against human breast cancer (T47D cell lines), it's *in vitro* cytotoxicity test was done by MTT ([3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay while the *in vivo* studies were done by xenografting female Balb C mice with human breast cancer (T47D) cell implantation into the mamae fat-pad and found that *Kaempferia rotunda* rhizome is potential to be developed as breast cancer chemotherapeutic agent.

Eswaraiah *et al* worked on leaf extract of *Avicennia alba (*mangrove plant) and by using GC-MS method the authors analyzed bioactive constituents of this plant[24]. The major compounds detected in the extract were phenolic compounds, terpenoids, di-terpene and tri-terpenes. These bioactive compounds were then tested for cytotoxicity against some cancer cell lines, and it was observed that the methanolic extract was cytotoxic against human breast adeno carcinoma (MCF7) and HeLa cell lines. Results obtained also confirm that the leaf extract showed higher anti-cancerous activity against HeLa cell lines as compared to MCF7 cell lines[24].

Di Meo *et al* worked on two grape varieties *Aglianico* and *Falanghina*[25]. The bioactive constituents obtained from seed were hydroxyl benzoic acids (salicylic & gentistic), hydroxyl cinnamic acids (caffeic, p-coumaric & ferulic), flavan-3-ols (catechin, epicatechin, gallocatechin, epi-gallocatechin, catechin-3-O-gallate, proanthocyanidins) and stilbene (viniferins, resveratrol). For seeing anti-cancerous activities, the authors used semi-polar extracts of these seeds and worked on a tumor that affects pleural surface called the malignant mesothelioma. From the results obtained it was confirmed that by accumulation of bioactive constituents such as: a proanthocyanidins and phenylpropanoid precursor, intrinsic apoptosis was induced in a dose and time dependent manner by seed extracts of both grapes varieties. This suggested the use of phenolic molecules from grape varieties against malignant mesothelioma alone as well as in combination with other natural products as well as chemotherapeutic agents.

The *Piper* species comprises bioactive constituents such as; piperine, pellitorine, chabamide, guineensine and piperlongumine. These bioactive compounds were found to induce apoptosis and are potent cancer cell proliferation inhibitors. They inhibit growth of cancer cell lines and were found to be effective against both malignant as well as non-malignant ailments[26].

Vlaisavljevic *et al* conducted a study on a flowering plant from bean family (Fabaceae) called Glycyrrhiza glabra (licorice)[27]. By using LC-MS-MS method; they isolated 40 bioactive constituents from leaves and roots (fresh & dried) of licorice. From the results obtained, it was revealed that these compounds possessed strong antioxidants and had anti-cancerous properties. The root and leaves extracts were found to exhibit considerable pro-apoptotic property on

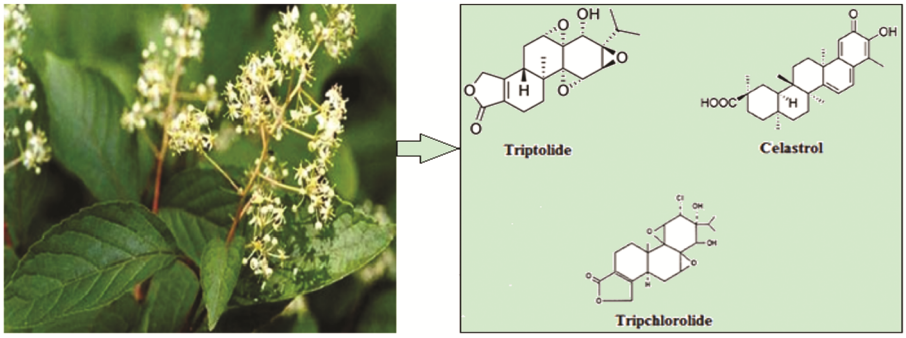

Fig. 10 — Representative image of *Tripterygium wilfordii,* and the active constituents present in *Tripterygium wilfordii*

ovarian (SiHa) cancer cell line and necrosis on breast (MDA-MB-361) adeno-carcinoma cell line.

A study by Huang *et al* revealed that anthrax quinones emodin and aloe-emodin are some other health enhancing compounds which were found to exhibit estrogenic activity just like phyto-estrogens and are abundantly found in *Rheum palmatum*[28]. Their study confirmed that these bioactive constituents are capable of suppressing ER*α* transcriptional activation and are responsible for down-regulating ER*α* protein levels, thereby inhibiting breast cancer cell proliferation. It was also observed that "aloe-emodin treatment" enhanced dissociation and ubiquitination of ER*α* and heat shocked protein (HSP90), while emodin was not able to induce/promote ER*α* ubiquitination and ER*α*/ HSP90 dissociation.

Tinospora cordifolia is a bulky, smooth and climbing deciduous shrub. The most commonly used part of this plant is stem which comprises several bioactive constituents such as; phyto-ecdysones, phenyl-propanoids, diterpene furan glycosides and norditerpene furan glycosides. *Studies have reported that, the extract of Tinospora cordifolia* possesses anticancer properties and killed HeLa cells *in vitro*[29].

Effect of processing on active constituents in plant-based food

According to researchers from Penn State's College of Agricultural Sciences, it is not adequate to assess the anticancer potential of plant-based food directly collected from the field, but the effect of harvesting methods, handling, storage, and preparation techniques should also be given equal importance. Similarly, researchers from the Center of Molecular Immunology and Infectious Disease, Huck Institute of Life Sciences, and Penn State Hershey Cancer Institute, demonstrated that in the next 20-years, new cancer cases are expected to rise 57% all over the world and also predicted that silver bullet treatment would not be an effective treatment against most of the tumors to emerge. Most of the studies suggest that intake of natural products (plant-based products as well as honey bee engineered products) can help preventing a variety of chronic ailments like cancers and their side effects. According to modern research, polyphenols, carotenoids, isothiocyanates and glucosinolates are the major bioactive compounds possess anticancer properties (Fig. 11). However, only limited data is available on using field-to-table function continuum on whole foods cancer preventive activities.

Brassica vegetables are rich source of phenolic compounds, beta-carotene, lutein, and zeaxanthin, *etc*., but the ways to prepare these vegetables have detrimental effect on nutrients and bioactive compounds. Studies reported that boiling have a great negative effect on the concentration of nutrients and pharmaceutically active compounds in *brassica* vegetables. Indoles and isothiocyanates in brassica vegetables were found to be potent cancer cell proliferation inhibitors in several cancers as researched on animal models including liver cancer, colon cancer, lung cancer, breast cancer, and stomach cancer. It has also been reported that, stir-frying is a good method to improve the health beneficial properties of cruciferous vegetables. For instance, broccoli is a rich source of beta carotene (15.6 mg/100 g) but content decreased after boiling

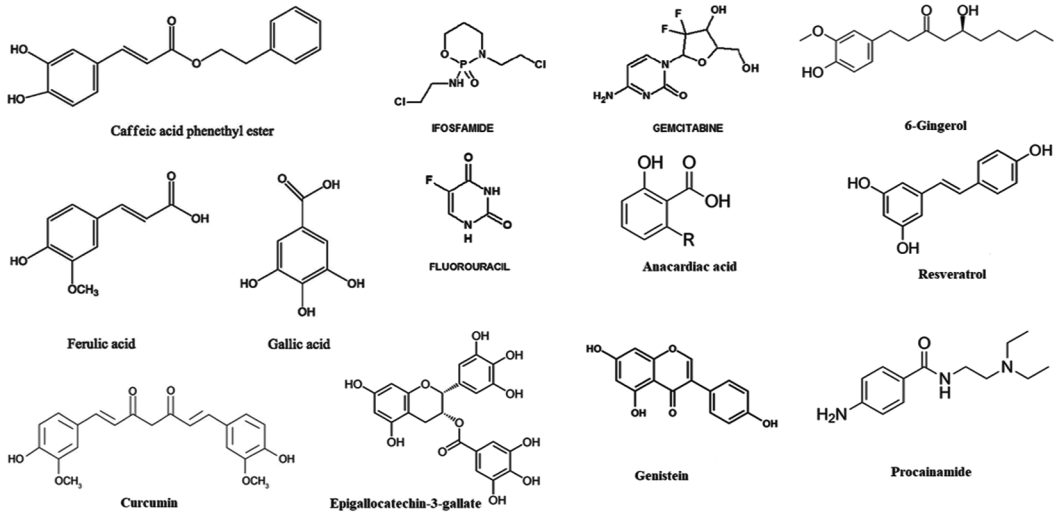

Fig. 11 — Major anticancer compounds from plants and their chemical structures

(12.86 mg/100g) while increased after stir-frying (16.36 mg/100g)[30]. Similarly, lutein, an important cancer preventive carotenoid, present in a significant amount in kale (43.66 mg/100g) increased by 40% after stir-frying[30]. On the other hand boiling is reported to be a best method for improving the carotene content in carrots. Boiling increased the carotene content by 25%. However, for tomatoes opposite trend was seen, as lycopene content decreased by 13%[30].

Curcuminoids, the active constituents of turmeric are highly sensitive to damage at high temperature. It has been reported that cooking lowered the antioxidant capacity of curcuminoids. In addition, the neuro-protective effects of cooked curcuminoids also got relatively lower when compared with parent curcuminoids[31]. Suresh *et al* also reported the loss of active constituents from some commonly used spices such as curcumin from *Curcuma longa*; capsaicin from *Capsicum annuum* and piperine from *Piper nigrum* when subjected to domestic cooking processes. Results showed 27-53% loss of curcumin, 18-36% loss of capsaicin,and 16-34% loss of piperine when subjected to cooking[32].

Similarly, changes in phenolic and phytosterol content in bamboo shoots during processing have also been investigated. Nirmala *et al* analyzed the phenolic content of soaked, boiled and canned shoots of *B. balcooa, B. tulda, D. giganteus,* and *D. hamiltonii* and found a significant decrease in the phenolic content of shoots (*Bambusa balcooa*, soaked: 72.27%, boiled: 70.30%, canned: 88.83%; *B, tulda*, soaked: 86.90%, boiled: 73.0%, canned: 84.85%; *D. giganteus*, soaked: 45.87%, boiled: 47.36%, canned: 76.86%; *D. hamiltonii*, 88.79%, 82.51% and 93.19%)[33]. Bajwa *et al* also determined the phenolic content of the shoots of four bamboo species, *viz*., *Bambusa nutans, Dendrocalamus giganteus D. hamiltonii,* and *D. latiflorus,* and found a notable decrease in the content after processing[34]. Hence, it is imperative to provide the knowledge about various processing techniques for preparation of food so that consumers can get maximum benefits of plant-based food and products.

Bioactive compounds from bacteria and animals

Besides plants, animals, marine organisms and microorganisms are also attractive source of therapeutic compounds that have mutagenic and oncogenic properties and can damage antibody synthesis or cell-mediated immune responses. Microorganisms produce a large variety of secondary metabolites and this characteristic makes them important target for pharmaceutical industry. For example, action bacteria, obtained from marine environment have gained substantial attention from researchers all over the world due to its therapeutic compounds profile. Bacterial proteins and peptides are promising bioactive constituents responsible for inhibiting cancer cell proliferation and can be used as potential anticancer drugs. Actinomycin D, bleomycin, doxorubicin, and mitomycin C are some of the examples already used as anti-cancerous antibiotics / therapeutics. One more anti-cancerous agent from bacteria, diphtheria toxin,is under clinical trials. Similarly, arginine deiminase, and p28 are under *in vitro* studies.

Micromonospora marina associated with a marine soft coral in the Indian Ocean was also found to be an important source of a novel depsi peptide named as thiocoraline, which was isolated from the mycelial extract of this bacterium in 1997. Thiocoraline has potential to inhibit DNA polymerase and is under clinical trials by "Pharma-Mar" a pharmaceutical company. Tendani *et al* identified and isolated endophytic bacteria (*Pseudomonas putida*, *Pseudomonas palleroniana, Pseudomonas cichorii*, *Pseudomonas* sp, *Arthrobacter pascens, Acinetobacter guillouiae*, *Bacillus safensis, Enterobacter asburiae,* and *Raoultella ornithinolytica*) form the leaves of *Crinum macowanii,* and investigated their anticancer properties against lung carcinoma cells (A549) and glioblastoma (U87MG) using MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxy-phenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay[35]. It was also found that, among all isolated endophytic bacteria, *Pseudomonas cichorii* showed highest inhibitory concentration while *Arthrobacter pascens* showed minimum inhibitory concentration. The crude extract of *Bacillus safensis* was also found to be effective against lung carcinoma cells (A549) and showed notable cell reduction (50%) at very low concentration (100 µg/mL)[35].

Furthermore, secondary metabolites production in microbial hosts through engineered methods has become interesting field of research and an attractive alternative platform because plant secondary metabolites do not meet the current demand because of low-yield, seasonal and geographical variations in chemical content and difficulty in quality control. Paclitaxel, artemisinin, berberine, quercetin, noscapine, naringenin and their precursors are some

important examples of engineered secondary metabolites[4]. Recently, Zhang *et al* demonstrated de novo production of catharanthine and vindoline, precursors from the plant *Catharanthus roseus*, for the production of vinblastine, an anticancer drug at an industrial scale[36]. Catharanthine and vindoline are monoterpene indole alkaloids present in the leaves of plant *Catharanthus roseus* and are difficult to synthesize chemically. This study demonstrated that microbial supply chains for essential medicines including vinblastine are viable solutions to secure the global or regional supply of important drugs, especially during unpredictable environmental events. These studies prove that production method through engineering is advantageous and has promising approach over the current methods and indicates that, in future microbes can replace the conventional drugs used against cancer therapies or they can be used in combination to enhance the effect of conventional drugs which makes them cost-effective.

Animals also produce bioactive compounds which are either essential for their own survival or produced integrally of more importance to other organisms. Like plants, bioactive compounds from animals can be used for treatment of various diseases and can be applied as dietary supplements after extraction and identification. Phakellistatin 10 and Phakellistatin 11 are the cytotoxic cyclic octapeptides isolated from marine sponge *Phakellia* sp. Pettit *et al* investigated the anticancer properties of Phakellistatin 10 and 11 and found that both compounds significantly inhibited growth of human cancer cell lines and lymphocytic leukemia (murine P-388)[37]. Similarly, Bashari *et al* by using MTT assay, studied anti-cancerous properties and cytotoxic analysis of ethanolic extract of *Stylissa carteri* and observed positive results against several cancer cell line such as; MCF-7, HCC-1954, MDA MB 468, SKBR3, and MDA MB 231. Cancer lines (HCC-1954) were used for conducting apoptosis assay and spheroid growth assay and observed that ethanol extract of *S. carteri* showed significant cytotoxic activity in breast cancer cells[38]. Ethanolic extract of this sponge also induces apoptosis spheroids growth was inhibited in HCC-1954 cells. Through GC-MS method some other bioactive compounds were identified such as 9,12-Octadecadienoic acid, 1, 2-Benzenediol, ethyl ester and Dibutyl phthalate.

The food items from animals like milk, meat and egg also protect the body against illness and furnish a wide range of nutritional bioactivities. Proteins, antibacterial peptides, lipids, and oligosaccharides are the bioactive compounds present in milk and improve the probiotic action. Similarly, bioactive compounds such as coenzyme Q10, omega-3 polyunsaturated fatty acids, carnitine, conjugated linoleic acid, carnosine, glutathione, lipoic acid can be obtained from meat. Eggs prevent age-related macular degeneration as they are also a good source of pharmaceutically important compounds like choline, lutein, zeaxanthin, phospholipids, and proteins.

Bioactive compounds from bee-products

In recent years, new studies revealed that researchers are interested in isolation and characterization of bioactive compounds from honey bee products which have been utilized as valuable products in nutraceuticals and pharmaceutics since ancient times[52]. Bee products can be divided into three categories such as; i) bee products derived from plants and modified by bees (propolis, pollen and honey), ii) bee products synthesized by bee's themselves through some secretary glands in their body (royal jelly, bee venom and beeswax), and iii) bee ecological bodies[53].

Among them propolis is a resinous sticky material produced by worker honey bees form plants exudates and utilized as embalming substance to protect colonies from external intruders and microorganisms and also provides thermoregulation by acting as a sealant[54-56]. Pollen is a male gametophyte, collected by worker honey bees mixed with their salivary secretions and used as food for brood[57]. Honey is produced by worker honey bees through ingestion and inversion of flowers nectar[58]. Royal jelly, a milky secretion from hypopharyngeal and mandibular gland of nurse honey bees, is utilized as a food for the queen for lifetime and also used to feed the developing larvae for first three days[60]. Bee venom also called apitoxin is produced by venom glands in the abdomen of worker/queen honeybee and it is utilized as defensive material. Bees wax comprises multifunctional role in a bee colony like; honeycomb construction, rearing of developing larvae/brood, food storage, and thermal insulation, etc.

These natural products are rich source of secondary metabolites/ bioactive compounds and it is not surprising that they have gained a lot of attention from researchers worldwide (Table 2). Among them, flavonoids and phenolic acids have the potential to inhibit tumor growth, its metastasis, and finally

Table 2 — Bee products and their bioactive compounds responsible for targeted anticancer properties.

Bee Products	Bioactive compounds	Target Cancer	Possible Mechanism	Reference
Bee pollen	Peptides	Breast cancer	Induction of apoptosis via caspase activation	[43]
Bee pollen	Anethole	Prostate cancer	Inhibitors of NF-KB, and apoptosis induction via TNF-α stimulation	[5]
Propolis	Pinocembrin	Breast cancer, colon cancer, leukemia model	Enhanced production of interleukin-10 and decreased production of TNF-aandIL-6	[44]
Propolis	Chrysin, galangin, coumaric acid	Tongue squamosa cancer	Activation of apoptotic cascadesvia caspase-3,-8and-9	[45]
Propolis	Chrysin, caffeica cid,*p*-coumaric acid, ferulic acid	Tongue squamosa cancer	Decreased level of prolinein cancer cells via prolinedehydrogenase/proline oxidase activity	[45]
Propolis	3-O-methylquercetin, chrysin, caffeic acid, CAPE, galangin, Pinocembrin	Carcinoma, lung adenocarcinoma	Cell cycle arrest via activation of p21	[46]
Propolis	chrysin, galangin, CAPE, benzyl ferulate, benzyl isoferulate, pinostrobin, 5-phenylpenta-2,4- dienoic acid, tectochrysin, phenolic acids, flavonoids	colon cancer, esophageal squamous cancer, gastric carcinoma cells, malignant melanoma cells	TRAIL-induced caspase activation and STAT3 inhibition in cancer cells	[5]
Honey (Chesnut honey)	3–2′-pyrrilonidinyl-kynurenic acid	Prostate cancer	Induction of apoptosis via caspase 3 activation	[47]
Honey	hesperidin, apigenin, acacetin, ellagic acid, chrysin,Caffeic acid, rosmarinic acid, luteolin, pinobanksin, pinocembrin, quercetin, galangin, wogonin, fisetin, kaempferol, myricetin	Colon cancer, Breast cancer	Inhibition of cell proliferation, inhibition of angiogenesis in cancer cells	[48]
Royal jelly	10-Hydroxy-2-decenoicacid	Breast cancer, colorectal cancer	Increased concentration of IL-2 and interferon(INF)-α; decreased level of IL-10	[49]
Bee venom	Melittin	Lung cancer	Induction of apoptosis, inhibition of invasion and migration of melanoma cells through interference of factinre-organization and epidermal growth factor receptor (EGFR) activity	[50]
Bee venom	Melittin	Gastric cancer, lung cancer	Inhibition of MAPK signaling pathway and mitochondrial pathway mediated apoptosis	[51]

apoptosis[39]. Honey bees, the master chemists and chemical engineer synthesize natural products which are excellent source of bioactive compounds. Bioactive compounds responsible for anticancer activities among bee products are peptide, monounsaturated and polyunsaturated fatty acids, anethole, flavonoids and polyphenols in bee pollen and bee bread (Fig. 12); pinocembrin, diterpenes, triterpenes, chrysin, galangin, coumaric acid, ferulic acid, 3-O-methylquercetin, caffeic acid and CAPE in propolis (Fig. 13); gallic acid, caffeic acid, syringe acid, chlorogenic acid *p*-coumaric acid, ferulicacid, catechin, quercetin, chrysin 3–2′-pyrrilonidinyl-kynurenic acid in honey (Fig. 14); 10-hydroxy-2-decenoicacid in Royal jelly, Mellitin, and phospholipase A_2 in bee venom[39] (Fig. 15). The molecular mechanisms for inhibiting cancer development via bioactive compounds in honey is by arresting cell cycle, apoptosis activation, oxidative stress modulation, release of cytochrome-C via activation of mitochondrial outer membrane permeabilization, insulin signaling pathway activation, amelioration of inflammation, and inhibition of angiogenesis. The anti-cancer effect of Melittin in bee venom is related to its antiangiogenic effect as demonstrated via inhibition of VEGF and hypoxia-inducible factor (HIF) signaling pathways.

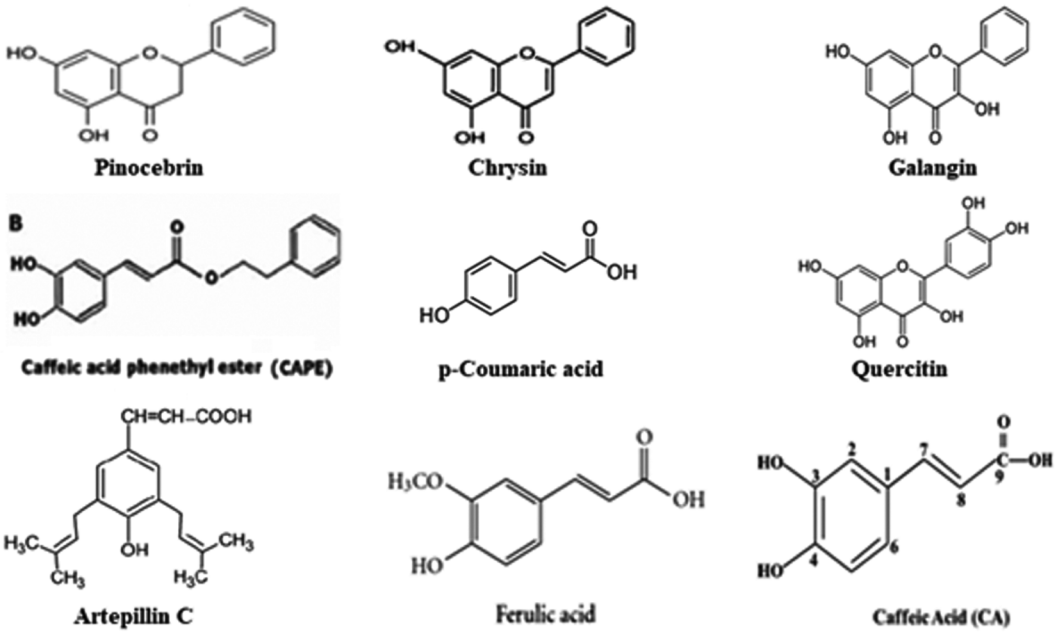

Fig. 12 — Bioactive compounds from bee pollen and bee bread with their chemical structures.

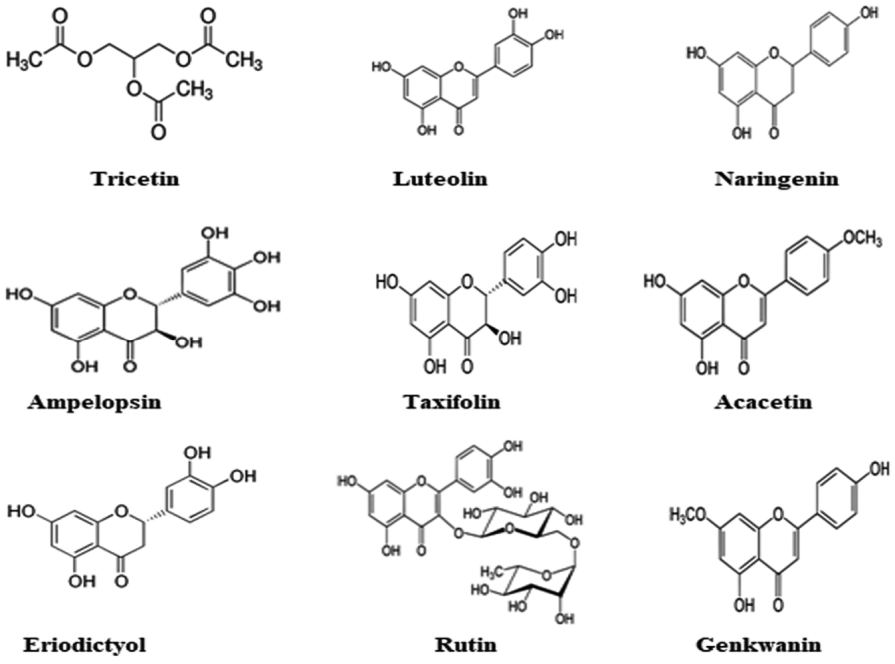

Fig. 13 — Bioactive compounds from propolis and their chemical structures

Phospholipase A2 promotes cancer cell apoptosis by an increase in reactive oxygen species (ROS) and a rise in intracellular Ca^{2+}, release of cytochrome C and caspase-3, resulting in DNA fragmentation; 10-hydroxy-2-decenoicacid active component of royal jelly-mediated cancer cell proliferation inhibition via secretion of cytokines by mononuclear cells. Additionally, polyphenols, genistein, curcumin, resveratrol, sulforaphane, isothiocyanates, silymarin, diallyl sulfide, lycopene, rosmarinic acid, apigenin, and gingerol show much promise to be developed as novel therapeutic agents in the fight against cancer.

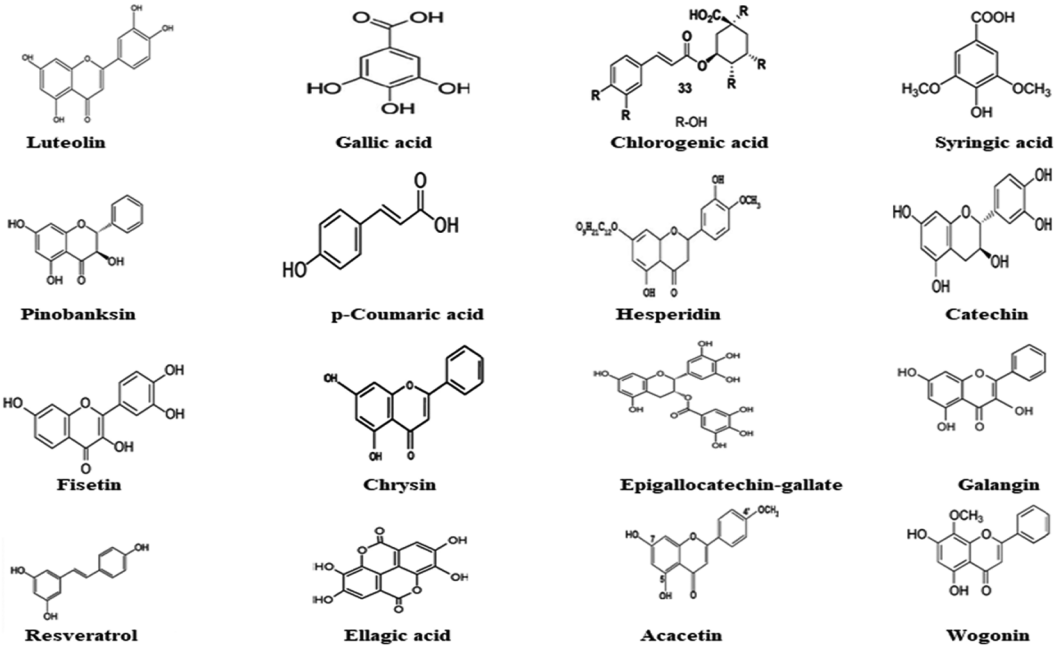

Fig. 14 — Bioactive compounds from honey and their chemical structures.

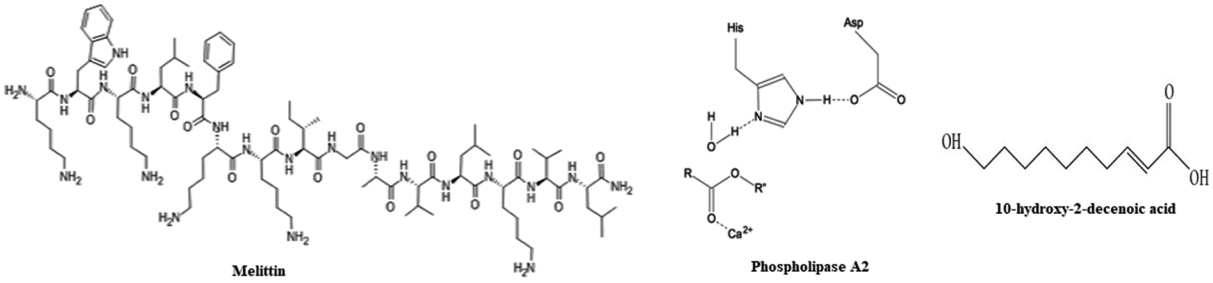

Fig. 15 — Bioactive compounds from bee venom and royal jelly with their chemical structure

Conclusion

Despite much research and progress in diagnosis and treatment of cancer, the prevalence and death ratios due to tumors are increasing worldwide. The drug resistance and side effects associated with cancer treatment awaken compelling remedial treatment options. Hence, search for anti-neoplastic drugs like alkylating agents, anti-metabolites, natural products from plants and animals, and anti-cancerous medicines are crucial part to be discussed. Among them bioactive compounds obtained from natural sources have significant therapeutic potentialities against cancer. They can impart critical role in cancer prevention and treatment. Although, a large number of pharmaceutically active compounds have already been characterized and isolated from plants, animals, honey bees, and microorganisms derived anticancer bioactive compounds still need to be explored with the advent of modern technology for development and their usage as future therapeutic agents against cancer in cost-effective manner.

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Conflict of interest

All authors declare no conflict of interest.

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