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Anticancer potential of medicinal plants from Bangladesh and their effective compounds against cancer

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Abstract
Cancer is a life-threatening disease which severely affects the people around the globe. There is a growing demand to secure a permanent cure to treat this nasty disease. The currently available techniques like chemotherapy are not feasible for their devastating post-treatment consequences and also not affordable to every person. Therefore, researchers always seek a new remedy for the permanent cure of this deadly disease. Different plant derived metabolites have become the center of interest due to their less side effects and multipurpose application in preventing cancer. With the success of these metabolites, new technologies are about to be developed which hopefully will lead the researchers to find a definitive cure. Bangladesh is an agricultural country and tremendous variety of medicinal plant is available here with significant anticancer property. This study has been designed to investigate different medicinal plants of Bangladesh with anticancer activity and their effective compounds to treat cancer.

Keywords: Anticancer, antitumor, medicinal plants, metabolites, Bangladesh

Introduction
Cancer is a life threatening disease which is characterized by the abnormal proliferation of human body cells. As a result of the abnormal proliferation, the normal function of the affected organ is severely disrupted which can lead to death of the patient [1]. Cancer is usually caused by the mutations in two types of genes- (1) oncogenes which induce cancer and (2) tumor suppressing genes which play a major role in suppressing tumor. Cancer cells usually spread throughout the body via blood vessels and lymphatic systems to metastasize. [2] Medicinal plants are being utilized as indigenous medicines from very beginning of the appearance of life on earth. In the world still 80% of total people specially those in the rural area are directly dependent on the medicinal plants due to their beneficial effects, less toxicity and less expensiveness than conventional diseases [3, 4]. Many plant derived natural metabolites or subtle modified metabolites exhibit anticancer property which provides positive indication of the effective use of these plants in therapeutic purposes [5, 6]. More than 700 medicinal plants are grown in Bangladesh and about 70 species among them has been shown to have anticancer property by laboratory phytochemical screening [7-8]. This study comprises 50 medicinal plants with anticancer properties from Bangladesh and their effective compound against cancer cells which hopefully will raise the researchers' interest in *in vitro* study.

Methods
This article has been designed by extensive reviewing of scientific ethnobotanical literature of most recent time by the authors.

Medicinal Plants with Anticancer Properties from Bangladesh
Allium sativum (Common Name: Rashun)
Allium sativum (garlic) is a herb of Amaryllidaceae family that is used as condiment in food. It has a long history of medicinal use from ancient time due to its multifunctional medicinal properties. The natural compounds of garlic such as diallyl sulfides, S-allylcysteine, S-allylmercaptocysteine are responsible for the cytotoxic and anticancer activity. The cultivation of garlic in the presence of selenium results in the production of orgnao-selenium compounds which are more effective in destroying cancer cell [9]. Allyl sulphides have modulatory effects on checkpoint modulators of cell cycle, such as cyclin□dependent kinase 1 (Cdk1) and cell division cycle 25 C (Cdc25 C) phosphatase by which it arrests the cancer cells at G_2/M phase of cell cycle [10].

In vitro application of aqueous garlic extract on HeLa cell line exhibits significant degrees of cytotoxic activity. 500 µL of garlic extract is capable of killing 95% of the cancer cells after 24 hours of incubation. Moreover, 400, 300, 200 or 100 µL of extract is capable of killing 92, 87, 60, and 24% of the HeLa cells [11].

***Aloe vera* (Common Name: Ghritkumari)**

Aloe vera is the member of Asphodelaceae family which has been used traditionally for versatile medicinal uses. This plant is enriched with numerous bioactive compounds such as Barbaloin, Anthrone-C-glycosides, Chromones, Campesterol, Lupeols etc. Different plant parts are effective in treating dysentery, diarrhea, ulcers, arthritis, diabetes, rheumatic fever and other complications. More than one phytochemical of this plant have been reported to have the antimutagenic activity [12]. The Aloctin I from the *Aloe vera* leaf pulp is capable of regressing the size of *Ehrlich ascites* tumors in mice. The antitumor activity of this compound has also been evidenced by prophylactic administration of Aloctin I which decreases the cancer effective markers such as Sialic Acid and Tumor Necrosis Factor Alpha (TNFα) [13]. The hydroxyanthraquinone called aloe-emodin (AE) from the plant leaf has antineuroectodermal tumor activity. This compound exhibits the antitumor activity by triggering programmed cell death. The culture of Neuroblastoma cells (IMR-32, IMR-5, AF8, and SJ-N-KP), pPNET cells (TC32), Ewing's sarcoma cells (TC106) in the presence of AE for 72 hours halts the proliferation of these cells at G_2/M phase of the cell cycle and suggests potential DNA damage leaving the cells to undergo apoptosis [14].

***Ananas comosus* (Common Name: Anaras)**

Ananas comosus (Pineapple) belongs to the family-Bromeliaceae, is an edible succulent fruit. The major bioactive compound of this plant is a crude extract called Bromalein which comprises proteinases, peroxidase, acid phosphatase and several protease inhibitors. These compounds have been reported to exhibit multiple therapeutic activities such as- control of tumor growth, control of diarrhea, inflammation, dermatological and skin debridement etc [15]. *In vitro* study of Intraperitoneal administration of Bromalein in animals transplanted with P-388, sarcoma S-37, Ehrlich ascites tumor cells (EAT), Lewis lung carcinoma cells (LLC), M-B16F10 (MB-F10) melanoma and ADC-755 mammary adenocarcinoma cells suggests both antimetastatic and anticancer activity. Antimetastatic activity of bromelain had been reported when doses of 50 and 12.5 mg/kg in LLC transplanted animal resulted in the reduction of metastatic foci between 85% and 74% respectively. The administration of the same compound can also increase the life span of P-388 infected animals between 140% and 169% depending on the Bromelain dose [16].

***Carica papaya* (Common Name: Pepe)**

Carica papaya (Papaya) belongs to the Caricaceae family, is the most commonly consumed fruit throughout the world. The exceptional nutritional and medicinal properties make it lucrative for the consumers. Various phytochemicals of Papaya plant such as- Papain, Lycopene and Isothyocyanate are effective for destroying cancer cells. Papain is an enzyme (EC 3.4.22.2) which exhibits the anticancer activity by cleaving the fibrin of cancer cell wall [17]. Lycopene arrests the proliferation of human prostate epithelial cancer cells at G0/G1 phase of cell cycle by modulating the Cyclin D protein expression [18]. Papaya plant aerial part extract has been reported to have anticancer property against TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cells. The ethyl acetate extract of the plant part is the most effective one which is capable of killing almost 63% MCF7 cancer cells within 48 hours [19].

***Coccinia grandis* (Common Name: Telakuch)**

Coccinia grandis (Ivy gourd) is the member of Cucurbitaceae family. This plant has a long history of use as household remedy for its potential medicinal uses. The most effective bioactive compounds of this plant include- Heptacosane, β – sitosterol, Taraxerone, Lycopene, β- Amyrin Acetate, Lupeol and Cucurbitacin B which mount protection and prevention strategies against various diseases. This plant has been shown to exhibit multiple medicinal properties like analgesic, antipyretic, anti-inflammatory, hepatoprotective, antimalarial, antidyslipidemic, anticancer, antitussive etc. [20]. The anticancer activity of Ivy gourd is partly due to the presence of Cucurbitacin B. Cucurbitacin B inhibits the activity of telomerase by down regulating hTERT gene expression and arrests the cell cycle progression at G_2/M phase in some form of cancer cells. The compound has also been reported to induce the apoptosis in cancer cells [21]. *In vitro* study with 200 and 400 mg/kg intraperitoneal injection of ethanol extract for 10 days in rats with Ehrlich Ascites Carcinoma (EAC) cell induced tumor suggested almost 30 and 97% increase in the lifespan respectively. The administration also showed the significant reduction of cancer markers and increment of body weight of the subject [22].

***Glycine max* (Common Name: Soya bean)**

Glycine max is the member of Fabaceae family which contains isoflavones, flavones and lignans which have effective anticancer activity. The major constituent among different isoflavons found in Glycine max is Genistein which is effective against a range of different cancers. Genistein has been reported to inhibit a number of proteins such as tyrosine kinase, topoisomerase II and s6 kinases which are major regulators of the cell division and differentiation. Moreover, the compound has also effective role in preventing the angiogenesis during the metastasis phase of the cancer.[23] Laboratory experiment with Bowman–Birk inhibitors (BBI) from *Glycine max* has been shown to arrest the growth of HT29 colon adenocarcinoma cells. Two major soybean isoinhibitors, IBB1 and IBBD2 exhibit their anticancer activity by blocking several metabolizing hormones like trypsin and chymotrypsin. The BBI treatment works in a dose dependent manner and blocks the cell cycle progression at G0/G1 phase [24].

***Momordica charantia* (Common Name: Karola)**

Momordica charantia (Bitter melon/gourd) is a type of vine that belongs to the Cucurbitaceae family. The medicinal value of Bitter melon is due to the presence of bioactive phytochemical constituents that protect the human body from numerous diseases by variety of physiological processes. Bitter gourd is a rich source of phytochemicals like flavanoids, saponins, terpenoids, coumarins, emodins, alkaloids, proteins, cardiac glycosides, anthraquinones, anthocyanins, steroids etc which have definite roles in combating diseases [25]. The seeds of *M. charantia* contain Ribosome Inactivating Protein (RIP) which blocks the protein synthesis causing the rRNA to depurinate. The chemical modification of this compound by Polyethylene Glycol (PEG)

conjugation results in even more effective cytotoxic agent (PEG-RIP). These compounds also stimulate the caspase-3 enzymes to induce apoptosis in cancer cells. The *in vivo* study of these compounds against A431 cancer cells showed that the cells were arrested at G_0/G_1 phase of the cell cycle [26].

***Terminalia arjuna* (Common Name: Arjun)**

Terminalia arjuna (Arjun tree) is the member of Combretaceae family which has long history of therapeutic uses. Major bioactive compounds of this plant include arjunone, arjunic acid, arjunolic acid, terminolitin, mirystyl oleate etc. [27]. The prominent cytotoxic agent of Arjun tree is a hydrolysable tannin called Casuarinin which usually occurs in the bark of the plant. This compound induces the p53-dependent kinase inhibitor protein (p21/WAF1) that arrests the cancer cells at G0/G1 phase linking the potential DNA damage. Casuarinin is effective in destroying A549 cancer cells by blocking the cell cycle progression which is followed by the induction of programmed cell death.[28] The Dimethylsulphoxide (DMSO) extract of *T. arjuna* bark is capable of inhibiting more than 70% growth in the liver (HEP 2) & colon (HT 29) cancer cell lines [29].

***Vitex negundo* (Common name: Nisinda)**

Vitex negundo belongs to the family Lamiaceae, is an aromatic shrub which has a long history of medicinal use for variety of purposes. It has been reported to possess potent pharmacological properties like anti-inflammatory, anti-rheumatic, antibiotic, hepatoprotective, antioxidant, anticonvulsant, anti-cancer etc. [30]. The major bioactive compounds of this plant include vitamin C, casticin; sabinene, lignans, nishindine, vitedoin-A; vitedoin-B etc. [31]. Evn-50 is a lignan compounds mixture extracted from *Vitex negundo* has potential anticancer activity against the Breast cancer cell line MDA-MB-435 and liver cancer cell line SMMC-7721. Laboratory experiment shows that the ethanol extract of that lignan triggers anticancer activity by arresting the cell at G2/M phase of the cell cycle and subsequently inducing apoptosis.

The evidence of the anticancer activity of Env-50 has been supported by the observations of increased phosphorylation of Histone 3 at Ser10, phosphorylation of Cdk1 at Tyr15, expression of cyclin B1, and decreased expression of Cdc25c of the cells after treatment with Env-50 [32]. Ethanol and aqueous extract of Vitex negundo has also been shown to increase the lifespan by 70-80% in laboratory cancer subjects with induced Dalton's Ascitic Lymphoma (DAL) [33].

***Zingiber officinale* (Common Name: Ada)**

Zingiber officinale contains gingerol-6 which is considered superior in combating cancer. It is a member of Zingiberaceae family which is commonly used as condiments in food. Gingerol-6 has two modes of anticancer activity- it suppresses the cancer cell growth progression and also blocks the supply of nutrients to the cancer cells by angiogenesis [34]. Laboratory experiment with the leaf extract from *Zingiber officinale* shows that it is effective in reducing the cell viability in human colorectal cells (HCT116, SW480 and LoVo cells). In addition to that, the extract has also been reported to induce apoptosis in cancer cells in a dose dependent manner. The evidence of apoptosis inducing ability has been confirmed by its ability to stimulate ATF3 expression in both mRNA and protein levels which is a major regulator of cell growth arrest and apoptosis in human colorectal cancer cells like HCT116 and SW480 cells [35].

Table 1: Additional medicinal plants with anticancer property and their effective compounds.

SL. No.	Species	Family	Common Name (English, Bengali)	Plant Part(s) Used	Effective Compound(s) against Cancer	Ref.
1.	*Acanthus ilicifolius*	Acanthaceae	Holy mangrove, Hargoza	Flower	Anthocyanins, lupeol, alpha amyrin, ursolic acid etc.	[36]
2.	*Acorus calamus*	Acoraceae	Sweet flag, Bach	Whole plant	Lectins, alpha-asarone , beta-asarone etc.	[37]
3.	*Andrographis paniculata*	Acanthaceae	Green chirayta, Kalomegh	Whole plant	Andrographolide and it's derivatives	[38]
4.	*Asparagus racemosus*	Asparagaceae	Asparagus, Shatamuli	Root	Steroidal saponins	[39]
5.	*Averrhoa carambola*	Oxalidaceae	Star fruit, Kamranga	Fruit	Flavonoid-AC1	[40]
6.	*Azadirachta indica*	Meliaceae	Indian lilac, Neem	Leaf	Azadirachtin, gedunin, nimbin, nimbidin, nimbolide, beta-sitosterol	[41, 42]
7.	*Bacopa monnieri*	Plantaginaceae	Water hyssop, Brahmishak	Shoot	Ferulic acid, chlorogenic acid, cucurbitacins etc.	[43, 44]
8.	*Brassica oleracea*	Brassicaceae	Cabbage, Badha-kopi	Cabbage leaves	Sulforaphane	[45]
9.	*Calotropis gigantea*	Apocynaceae	Gigantic Swallow wort, Akand	Leaf, flower	Cardenolid, calotropin, calotropogenin, anhydrosophoradiol-3-acetate etc.	[46]
10.	*Camellia sinensis*	Theaceae	Tea , Chai	Leaf	Epigallocatechingallate, gallic acid, and quercetin.	[47]
11.	*Cassia fistula*	Fabaceae	Golden rain tree, Sonalo	Flower	Rhein	[48]
12.	*Cinnamomum tamala*	Lauraceae	Bay leaf, Tejpata	Leaf	Bornyl acetate, caryophylene oxide	[49]
13.	*Citrus aurantium*	Rutaceae	Bitter orange, Komlalebu	Fruit peel, fruit	Limonene, vitamin C	[50]
14.	*Curcuma longa*	Zingiberaceae	Turmeric, Holud	Rhizome	Curcumin (diferuloylmethane)	[51]
15.	*Cuscuta reflexa*	Convolvulaceae	Giant dodder, Swarnolata	Whole plant	Scoparone, *p*-coumaric acid, stigmasta-3,5-diene, 1-*O*-*p*-hydroxycinnamoylglucose	[52, 53]
16.	*Datura metel*	Solanaceae	Datura, Dhutra	Leaf, stem and other parts	Steroidal lactones- withonilides	[54]

17.	*Dysoxylum binectariferum*	Meliaceae	White cedar , Mahogany	Stem bark	Rohitukine	[55]
18.	*Ficus carica*	Moraceae	Fig , Dumur	Fruit	Arabinose, beta carotines, xanthotoxol, glycosides etc.	[56]
19.	*Glycyrrhiza glabra*	Fabaceae	Licorice, Yashthimadhu	Root	18- beta glycyrrhetic acid	[57]
20.	*Hibiscus rosa-sinensis*	Malvaceae	Chinese hibiscus, Jaba	Leaf	Riboflavin, niacin, margaric acid, lauric acid etc.	[58]
21.	*Hygrophila auriculata*	Acanthaceae	Starthorn, Talmakhna	Leaf, flower and other parts	Stigmasterol, luteolin, betulin, lupeol etc.	[59]
22.	*Hyptis suaveolens*	Lamiaceae	Wilayatitulsi, Tokma	Leaf	Sabinene, beta- caryophyllene, Spatulenol etc.	[60]
23.	*Justicia adhatoda*	Acanthaceae	Malabar nut , Vasaka	Whole plant	Vasicine	[61]
24.	*Mangifera indica*	Anacardiaceae	Mango, Aam	Leaf	Mangiferin	[62,63]
25.	*Nelumbo nucifera*	Nelumbonaceae	Indian lotus, Padma	NA	Liensinine, Nuciferine	[64]
26.	*Phyllanthus emblica*	Phyllanthaceae	Indian gooseberry, Amlaki	Fruit	Corilagin, pyrogallol, chebulagic, gallic acid etc.	[65]
27.	*Plumbago zeylanica*	Plumbaginaceae	Doctorbush, Chita	NA	Plumbagin	[66]
28.	*Psidium guajava*	Myrtaceae	Guava, Peyara	Leaf , fruit	Ascorbic acid, apigenin, lycopene, rhamnoallosan	[67]
29.	*Punica granatum*	Lythraceae	Pomegrante, Dalim	Fruit	Punicalagin, pomegranate tannin, ellagitannins, urolithins	[68]
30.	*Rauvolfia serpentina*	Apocynaceae	Devil pepper, Chandra / Swarpagandha	NA	reserpine	[69]
31.	*Senna occidentalis*	Fabaceae	Coffee senna, Kalkashundi	Leaf	Tannins	[70]
32.	*Solanum lycopersicum*	Solanaceae	Tomato, Bilati begun	Fruit	Lycopene	[71]
33.	*Syzygium aromaticum*	Myrtaceae	Clove, Labanga	Flower bud	Betulinic acid and other triterpenes	[72]
34.	*Tagetes erecta*	Asteraceae	Marigold, Gendaphul	Flower	Quercetagetin, patuletin	[73]
35.	*Tamarindus indica*	Fabaceae	Tamarind, Tetul	Seed kernel	Polysaccharide PST001	[74]
36.	*Terminalia chebula*	Combretaceae	Chebulicmyrobalan, Haritaki	Fruit	Phenol , Palmitic acid	[75]
37.	*Trichosanthes kirilowii*	Cucurbitaceae	Chinese cucumber, Lota-mohakaal	Root	Trichosanthin	[76]
38.	*Withania somnifera*	Solanaceae	Indian ginseng, ashwagandha	Leaf, root	Withaferin A , withanolides	[77, 78]
39.	*Xanthium strumarium*	Asteraceae	Common cocklebur, Ghagra	Fruit	Xanthanolide sesquiterpene lactones, xanthatin etc.	[79]
40.	*Xylocarpus granatum*	Meliaceae	Puzzle fruit tree, Dhundul	Bark	Gedunin	[80]

Discussion

There are lots of medicinal plants available in the nature that exhibit significant anticancer properties. Different plants employ their characteristic anticancer properties by different mechanisms. And different plants are effective against different cancer cell lines. A well-directed research or modification of the natural compound (s) may be required to find out the best possible treatment of cancer.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of the manuscript.

Conclusion

Hopefully one day the plant derived metabolites will be the permanent medication for the cancer to be eradicated.

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