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Secondary Metabolites of Solanaceae and their Anti-Cancer Potential: An Overview

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Short Commentary

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About 85,000 valuable medicinal plant species are reported world-wide [1,2]. Many researchers have examined long-established uses of medicinal plants but only a few studies led to the development of novel drugs for the treatment of different ailments. India is the largest producer of medicinal plants and is rightly called the "Botanical garden of the World". Medicinal plants have been stated to comprise about 8000 species and account for approximately 50% of all the higher flowering plant species of India[3]. In other words, there are about 400 families of the flowering plants; at least 315 are represented by India [4,5].

Cancer continues to be one of the major causes of death worldwide and only modest progress has been made in reducing the morbidity and mortality of this disease [6]. Cancers may be caused in one of three ways, namely incorrect diet, genetic predisposition, and via the environment [7]. As many as 95% of all cancers are caused by life style and may take as long as 20–30 years to develop. Current estimates from the American Cancer Society and from the International Union Against Cancer indicate that 12 million cases of cancer were diagnosed last year, with 7 million deaths worldwide; these numbers are expected to double by 2030 (27 million cases with 17 million deaths) [8,9].

By definition, cancer is uncontrollable proliferation of cell. Cancer is of many types which have been named based on the type of cell affected with [10]. Cancer is also known as malignant tumor or benign tumor which has been classified based on the spread of disease. Benign tumors do not spread to other parts of body whereas malignant has high rate of proliferating to other parts [11]. In general, cell division takes place as per the body requirements where the old cells will die and removed from the body. But when cancer develops, this cell division will takes place continuously [12]. As cells become more and more abnormal, old or damaged cells survive when they should die, and new cells form when they are not needed. These extra cells can divide without stopping and may form growths called tumors. As per

the reports available, only 5-10 % of cancer occurrence is because of genetical defects and about 90-95% have their roots lies in lifestyle and environmental conditions [13]. Life style factors include cigarette smoking, alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity [14].

Anticancer drugs discovered from herbal medicines have a long history and plant-derived compounds have been an important source of several useful anti-cancer agents in clinical practice, such as vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, which are isolated or derived from *Catharanthusroseus* G. Don. (Apocynaceae), *Camptothecaacuminata*Decne (Nyssaceae), *Podophyllumpeltatum*Linnaeus (Podophyllaceae) and *Taxusbrevifolia*Nutt. (Taxaceae) [15]. A number of *Solanum*species have previously been investigated for their cytotoxicity,antioxidant and antiviral activities, and treatment of protozoal infections [16-19]. In addition antimicrobial, radical scavenging, cytotoxic and nematicidal activities and asthma treatment of some *Datura* species have been reported [20-24]. These studies have shown the potential of effectiveness of the plant species from Solanaceae family especially in cytotoxic and antioxidant activities.

This ethno botanical review was embarked upon to identify the various plants of *Solanaceae* family used in the traditional preparations for the management of Cancer and thereafter provide more information to the growing knowledge about the effective use of these local herbs. The medicinal value of these plants lies in some chemical substances they contain that produce a definite physiological action on the human body [25].

RISK FACTORS OF CANCER

Tobacco

Tobacco is the primary cause of lung cancer and ever since efforts are going on to reduce tobacco consumption [26]. In addition, about 25-30% of deaths occur due to tobacco consumption. It consists of 50 compounds which are highly carcinogenic like tobacco metabolite, benzopyrenediol epoxide, has a direct etiologic association with lung cancer and causes many behavioral problems [27]. The prevalence of ever smoker among adolescents was found to be 28.6% (21.2% males and 7.4% females), and current smokers were 17.2% (13.3% males and 3.8% females) [28]. Accelerated tobacco control programmers may aid to reduce rates of tobacco-related cancer mortality[29,30].

Alcohol

It is a widely known fact thatmost of the diseases attributable to alcohol is substantial, despite low diagnosis and treatment rates in many countries [31]. Alcohol is the second cause of esophageal cancer includingcancers of the oral cavity, pharynx, hypo pharynx, larynx, and esophagus [32]. The direct mechanism behind how alcohol contributes the cancer is not well understood but acetaldehyde and free radicals are produced as metabolic product of ethanol which proliferates the occurrence of cancers [33,34].

Infectious agents

Human papillomavirus, Epstein Barr virus, Kaposi's sarcoma-associated herpes virus, human T-lymphotropic virus 1, are associated with risks for various cancers like cervical cancer, anogenital cancer, skin cancer, nasopharyngeal cancer, Hodgkin's lymphoma, Kaposi's sarcoma, liver cancer[35-38]. The mechanism beyond the cause of cancer is becoming more evident that infection related inflammation is the major risk associated with. So agents which block this inflammation can be the alternative for the treatment [39].

Treatment of cancer and role of medicinal plants

Plant extracts showed significant antioxidant activity which could also help in antiinflammatory, anticancer, immunomodulatory, mucus secreting, cytoprotective etc [40].
There are many novel strategies have been developed for the treatment of cancers. However the therapy is associated with many adverse effects. Hence herbal drugs can be best alternative to avoid side effects associated with [41].
However, studies prove that plants belonging solanaceae have shown good anti cancer activity and below is the description.

Solanaceae

The Solanaceae are the third most important plant taxon economically and the most valuable in terms of vegetable crops, and are the most variable of crops species in terms of agricultural utility [42]. As it includes the tuber-bearing potato, a number of fruit-bearing vegetables (tomato, eggplant), ornamental plants (Petunia, Nicotiana), plantswith edible leaves (Solanumaethiopicum, S. macrocarpon) and medicinal plants (eg. Datura, Capsicum). Some Solanaceae plants are important model systems for biology; these include tomato for fruit ripening and plant defense, tobacco for plant defense, and petunia for the biology of anthocyanin pigments [43,44]. The solanaceae family consists of approximately 98 genera and some 2,700 species, [45,46] with a great diversity of habitats, morphology and ecology. The name Solanaceae derives from the genus Solanum, "the nightshade plant". The etymology of the Latin word is unclear. The name may come from a perceived resemblance of certain solanaceous flowers to the sunand its rays and infactone species of Solanum (Solanumnigrum)is known as the "sunberry". Alternatively, the name could originate from the Latin verb solari, meaning "to soothe", presumably referring to the soothing pharmacological properties of some of the psychoactive species of the family.The family is alsoinformally knownas thepotato family [47]. With theexception of tobacco (Nicotianoideae)and petunia(Petunioideae) most of theeconomicallyimportantgeneraare contained inthe sub-family Solanoideae.

Few Anticancer Plants of Nightshade Family

Capsicum frutescens:(Common name: Chilli pepper)

Capsaicin, one of the naturally occurring phytochemicals, is the major pungent constituent of hot chilli peppers of the genus Capsicum, which are extensively used as a food additive. It has been shown that capsaicin is involved in several physiological and pharmacological effects [48]. For example, several reports show that the use of capsaicin can relieve inflammation and pain associated with some diseases and cancer [49,50]. In addition, accumulating studies have shown that capsaicin has anti-proliferative effects on various human cancer cell lines including those derived from leukemia, multiple myeloma, cutaneous cell carcinoma, glioma, tongue cancer, nasopharyngeal carcinoma, esophageal carcinoma, gastric cancer, pancreatic cancer, hepatocarcinoma , colon carcinoma, non-small cell lung cancer, breast cancer and prostate cancer [51-54]. The capacity of capsaicin to suppress the growth of these cancer cells is primarily mediated through induction of apoptosis. Additionally, capsaicin-induced anti-cancer effects include the arrest of cell cycle progression, regulation of transcription factor expression, and suppression of growth signal transduction pathways. The apoptosis of Mouth Epidermal Carcinoma (KB) cells treated with capsaicin is associated with the induction of caspase 3 and 9, as well as dissipation of the mitochondrial membrane potential [55].

Cyphomandrabetacea (Cav.) Sendtn: (Common name: Tree Tomato)

C. betacea is domesticated plant in the hills of Darjeeling and the fruit has significant amount of bioactive phytochemicals like carotenoids, anthocyanins and phenolic compounds. Lycopene is the main carotene, accumulated significantly in ripe tomato fruits [56]. This pigment is a powerful natural antioxidant that acts as most efficient singlet oxygen quencher in vitro among common carotenoids and plays a determinant factor in reducing the mortality from several cancers [57]. Phenolic compounds are very important plant constituents because they exhibit antioxidant activity by inactivating lipid free radicals, or by preventing the decomposition of hydroperoxides into free radicals [58]. Cytotoxicity on Human breast cancer cell lines (MCF-7 and MDA-MB-231) is tested and found to be effective [59-64].

Daturametel L:(Common name: Indian Thorn apple)

Nitrogen-containing polyhydroxylated heterocyclic compounds are competitive inhibitors of various glycosidases, found most effective against various diseases including diabetes, cancer, and viral infections, along with additional activities, such as immunomodulatory properties and inhibition of glycolipid synthesis [65]. Withanolides was isolated from D. metel which are a group of steroidal lactones, many of thesecompounds exhibit a variety of biologicalactivities, including anti-inflammatory,antioxidant, antitumor, and immunosuppressive properties [66]. Withanolides can inhibit tumor cell proliferation and angiogenesis and induce the phase II enzyme quinonereductase [67]. Three withanolide glycosides nameddaturametelins, daturataturin and 7, 27-dihydroxy-1-oxowitha-2, 5, 24-trienolide, were isolated from the methanolic extract of the aerial parts of DaturametelL [68]. All compounds were tested for their antiproliferative activity towards the human colorectal carcinoma (HCT-116) cell line and are found to be effective [69-72].

Nicotianatabacum:(Common name: Tobacco)

Nicotine is a pyrrolidine alkaloid produced in large quantities in the tobacco plant (Nicotianatabacum) and had recently gained attention as a backbone for novel potentialalkaloids to be used for certain diseases like Cancer [73-75]. Tobacco plants were examined as a potential new source of cancer- preventive agents using an assay of inhibition of TNF-α release from cells [76]. Expression of TNF- α gene is regulated by various transcription factors, such as AP-1 and NF-κB [77,78]. It is proved that reduction of TNF- α expression in cancerous tissue leadsto inhibition of cancer development, and probably to preventionof cancer.Inhibition of TNF- α expression is associated with inhibitionof interleukin IL-1, IL-6, and IL-10 expression [79].Administration of tobacco leaf extract into mouse stomach inhibitedtumor development in subcutaneous tissue associated witha reduction of serum concentrations of TNF- α, IL-1 andIL-6, suggesting that it also inhibits cachexia intumor-bearing mice. Since tobacco leaf extract is nontoxicto mice, it might represent a new lead compound forcancer preventive agents [80].

Withaniasomnifera:(Common name: Aswagandha)

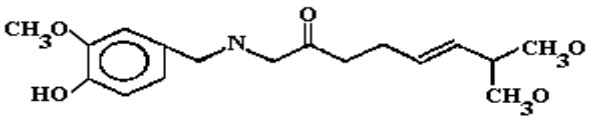
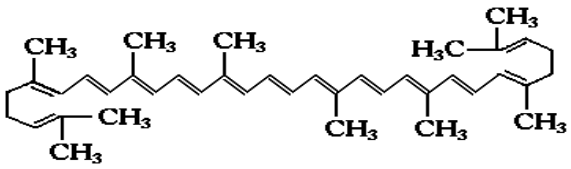
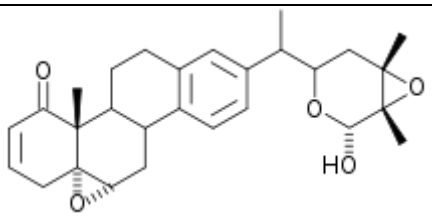
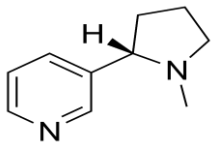
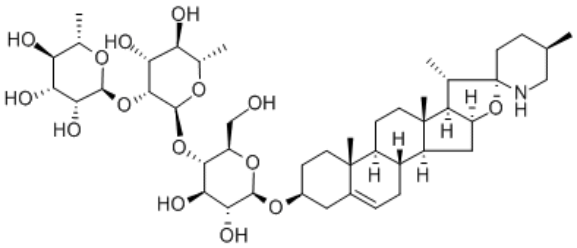
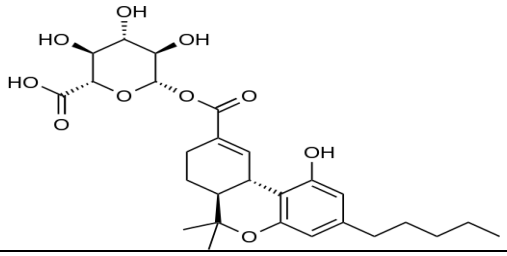
Ashwagandha is also described as an herbal tonic and health food in Vedas and considered as Indian Ginseng in traditional Indian system of medicine. Ashwagandha is an important medicinal plant, widely as home remedy for several diseases in India as well as other parts of the world [81]. Withanolides isolated from Withaniasomnifera, are similar to ginsenosides (theactive principles of Panax ginseng) in bothstructure and activity[82]. Withanolides(including Withaferin A, Sitoindoside IX, Physagulin D, Withanoside IV andViscosalactone B) inhibit growth & spread of various cancers such as cancers of thebreast, lung, colon and central nervous system due to their antiproliferative andantiangiogenic properties [83]. Withaferin-A (the most important withanolides) inhibit growth& spread of various cancers including that of the breast, cervix, colon, prostate, nasopharynx, larynx, malignant ascites and sarcomas by inducing apoptosis. Withaferin A is effective in both androgen-responsive and androgen-refractory prostate cancers [84]. Sitoindosides VII-X and Withaferin A have strong antioxidant, antistress, immunomodulatory, anti-inflammatory andantiaging properties. Withanolide D inhibits the metastatic colony formation in the lungsby malignant melanoma.Ashwagandhanolide, a new dimericwithanolide, isolated from Withania somnifera, inhibits growth & spread in cancers of breast, stomach, colon, lung and central nervous system.Withaniasomniferaalso possesses immunoenhancing,haemopoietic and neuroprotective properties and reduces side effects of radiotherapy &chemotherapy [85].

Solanum anguivi: (Common name: Children's tomato)

Solanum anguivi is a non tuberous and widely distributed plant with various medicinal properties. The cancer cell lines were used as the invitro model for the study of human hepatocytes [86]. The cytotoxic HEpG-2 (a human liver carcinoma cell line) and MCF-7 (breast cancer cell line) cell lines were selected for analyzing the antiproliferative activity of Solanum anguivi leaf ethyl acetate extract [87]. These cells were found to be suitable models to study the intracellular trafficking since because of their high degree of morphological and functional differentiation.

Solanum incanum: (Common name: Indian Nightshade)

Solamargine, purified from Chinese S. incanum possessed a potent cytotoxicity to human hepatocytes and normal skin fibroblasts leading to cell apoptosis by changes of cell morphology and DNA content [88] (Table1).

Herb- Compound	Structure
Capsicum frutescens- Capsaicin	
Cyphomandrabetacea- Lycopene	
***Daturametel* L**- Withanolide	
Nicotianatabacum- Nicotine	
Solanumincanum- Solamargine	
Solanumlyratum- Glucuronide	

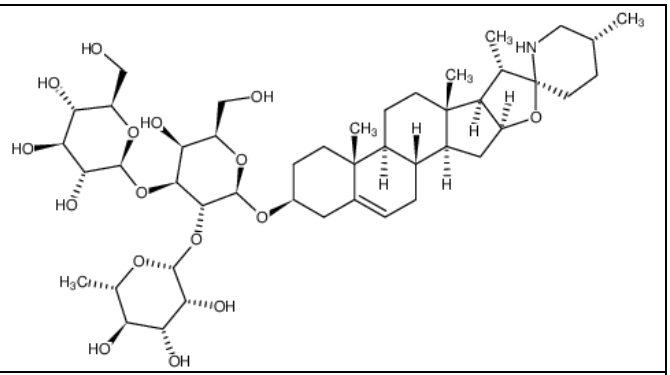
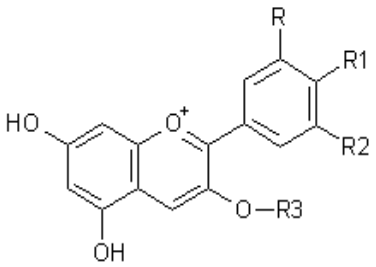
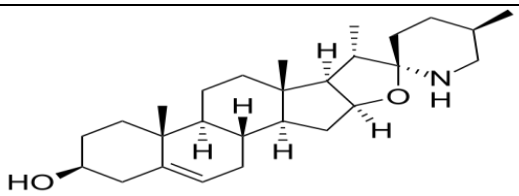
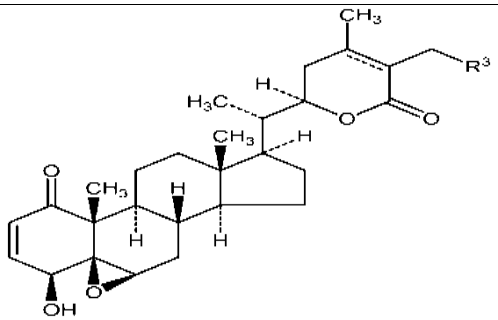
Solanumnigrum- Solasonine	
Solanum tuberosum L. var. Vitelotte- Anthocyanins	
Solanumxanthocarpum- Solasodine	
Withaniasomnifera- Withaferin A	

Table 1: Active Chemical constituents and their structure

CONCLUSION

Solanaceae family is characteristically ethnobotanical, that is, extensively utilized by humans. It is an important source of food, spice and medicine. The importance of Solanaceae family is due to the presence of alkaloids among their secondary metabolites, being known for their high alkaloid content. Alkaloids are found in all plant parts like roots, stems, leaves, flowers, fruits and seeds and are known for their antimicrobial activity [89]. However, some alkaloids show toxicity to humans and animals ranges from mildly irritating to fatal in small quantities [90,91]. Beside this, chemical constituents such as flavonoids, tannins and steroids were also found and are important secondary metabolites. Many plants belonging to the Solanaceae family have been used as a source of pharmaceuticals for centuries due to the presence of tropane and nicotine alkaloids, as principle actives [92-95]. Some Solanum-genera plants have traditionally been used as anti-cancer and anti-herpes agents from olden times [96-100].

The present article shows that the research based on historic literature can be an important tool on the selection of Solanaceae plants with biological activity. This article also pointed the great medical importance of the taxonomic update in Solanum species cited in historic literature researches.

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