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THE POTENTIAL APPLICATIONS OF PLANT-BASED ANTI-CANCER COMPOUNDS AND THEIR CHEMICAL DERIVATIVES

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ABSTRACT: Cancer has evolved as a detrimental disorder alongside cardiovascular diseases. Plant-derived natural products have been the most successful source of potential anti-cancer drugs and for the isolation and characterization of novel compounds. Till now, only about 10% of the world's biodiversity has been assessed for biological activity and numerous useful natural lead compounds are expected to be discovered in the near future. The exploration for anti-cancer agents from plant sources commenced in 1950s with the discovery of alkaloids; vinblastine and vincristine from *Catharanthus roseus* and the segregation of the cytotoxic podophyllotoxins from *Podophyllum peltatum*. Subsequently, paclitaxel or taxol was isolated from *Taxus brevifolia* bark and camptothecin was isolated from *Camptotheca acuminata*. Likewise, homoharringtonine, elliptinium, combretastatin A-4 betulinic acid, pervilleine-A, silvesterol, schischkinnin, and montamine are some of the other effective plant-originated anti-cancer compounds. With the developments in structural chemistry, a range of synthetic and semisynthetic lead compounds were designed and developed in laboratories. For instance, the semisynthetic analogues of vinca alkaloids are vinorelbine and vindesine, which are used either alone or in combination to combat several cancer types. Similarly, docetaxel, favopiridol, and roscovitine are some other plant-derived synthetic compounds from computational and combinatorial chemistry. In general, natural drugs are very safe, effective, and do not cause associated side effects when compared to synthetic compounds and hence, most preferred to combat cancers. Here we have summarized the applicability of plant-derived natural and their synthetic compounds considering the current practices and future perspectives in cancer therapies.

INTRODUCTION:

Plant-Derived Drugs History, Discovery, Challenges and Significance: Medicinal system of Mesopotamia comprised of about 1000 plant-derived medicines; Egyptian medicines and Traditional Chinese Medicine (TCM) have been extensively documented over the past thousands of years [1]. The written records of Ayurveda, the Indian medicinal system, originated before the 1st millennium BC [2].

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However, logical drug discovery from plants commenced at the beginning of the 19th century, when Friedrich Serturner successfully extracted an analgesic and sleep-inducing agent from the Opium poppy, themorphium (morphine) that, was named after Morpheus, the Greek god of dreams. He thoroughly discussed isolation, crystallization,

crystal structure, and pharmacological properties of morphine that was studied first in dogs and then in self-experiments [3]. Parallel to this, many bioactive natural products, and main alkaloids such as caffeine, nicotine, codeine, quinine, colchicine, cocaine, capsaicin, and atropine were isolated from their natural sources and were studied in-depth. Salicylic acid (derived from plant *Salix alba*) was one of the first natural compounds to be generated by chemical synthesis in 1853 [4]. During year 1981 to 2010, about 1073 new chemical entities and small molecules were approved by regulatory authorities, among which only 36% were purely synthetic or chemically derived, while more than 50% were derived from natural sources [5].

Challenges Contributing to the Decline in Research Interest Towards Natural Products: Ambiguity in nomenclature (*i.e.*"*Amrita*" is being used to describe *Tinospora cordifolia* Willd Miers as well as *Phyllanthus emblica* L.) of medicinal plants described in Ayurvedic texts adds to confusion which encourages the practice of substitution of spurious drug material in place of genuine raw material.

One of the greatest set back in exploring plant-based compounds is adulteration, which led to the declined research interest in plants derived compounds. The utilization of adulterants is a common malpractice in the herbal raw material trade owing to easy availability of substandard drugs, lack of adequate regulatory vigilance in this aspect. Many substitute drugs are also mentioned in Ayurvedic texts, which add to more uncertainty in the selection for drug research. The criterion in selection of substitute drug is based on similarity of properties (*Rasa*, *Guna*, *Virya* and *Vipaka*) and therapeutic action (*Karma*). The twenty-four (24) most commonly used substituted drugs in Ayurveda have been mentioned by Bucar *et al.*, 2013 [6]. For an explicit identification, a combinatorial approach *viz.* incorporating genetic and chemical analysis besides morphological and anatomical characterization, is necessary [7].

Regeneration of the Interest in Natural Products-Dependent Drug Discovery: The plant kingdom has numerous species; that produce an array of bioactive compounds having various chemical scaffolds. Previously only 6% of existing plant species had been systematically investigated for their pharmacological potential, and only around 15% had been evaluated phytochemically [8]. Due to ongoing research efforts, the number of well-characterized and studied plants is constantly increasing. Yet there are many plant-based compounds that are not well explored pharmacologically among almost 3, 10, 000 plant species that are described so far (IUCN 2015) [8-9].

The remarkably lower number of chiral centers, lower size, and higher flexibility culminates in weaker and less specific activity of synthetic compounds;. At the same time, natural products often have specific biological actions due to their binding affinities for specific protein receptors for their relevant biological functions, possess superior chemical diversity and complexity [10]. Since, living organisms make natural products, they evolve with their creator, accumulating evolutionary properties optimized for serving specific biological roles (*e.g.*, binding to specific targets) [11].

Cancer: Cancer is a set of disorders characterized by abnormal cell growth and can conquer and escalate to other body parts [12]; the latter process is referred to as metastasizing. Metastases's leading to mortalities is a salient feature of cancer. Possible signs and symptoms include lump, abnormal bleeding, prolonged cough, uneven weight loss, and changes in bowel movements (NCI, what is cancer). Tobacco use, obesity, poor diet, lack of physical activity, and excessive drinking of alcohol are some of the major causes [13]. Other factors include hepatitis B, hepatitis C, human papillomavirus infections, environmental pollutants, and exposure to ionizing radiation [14]. Cancer is classified by the organelle it affects. The types of cancer include carcinoma, sarcoma, lymphoma and leukemia, germ cell tumor, and blastoma [15].

Cancer accounts for approximately 8.8 million deaths (the year 2015) which is 13% of total deaths occurring globally. The most common cancers are stomach (0.754 million deaths), lung (1.69 million deaths), liver (0.788 million deaths), breast cancer (0.571 million deaths), and colorectal (0.774 million deaths). This explains how cancer has become the primary cause of death in developed countries and the second leading cause in

developing countries [16]. The common approaches for treating cancer are radiation therapy, chemotherapy, immunotherapy, targeted therapy (monoclonal antibody therapy), hormone therapy, stem cell transplant, and precision medicine. The choice of therapy out of these is determined by the grade and location of the tumor, the disease stage as well as the prospect of the patient. All these approaches are routinely used (either solely or in combination) for cancer treatment and have proven their merit; however, the resulting side effects cannot be overlooked.

Indian Medicine Systems: There is no direct reference of cancer as a separate disease in the classical literature of Ayurveda. It can be correlated with some inflammatory or non-inflammatory swelling; either as *Granthi* (minor neoplasm) or *Arbuda* (major neoplasm). The three bio-energies namely *Vata*, *Pitta* and *Kapha* are crucial for maintaining normal bodily functions. All the disorders wherein a set of particular stage is referred to as *Asadhya* (untreatable) or *Yapya* (difficult to treat/ conservative management) peculiarly in later worsening stage of *Arsha*, *Visphota*, *Raktapitta*, *Vidradi*, *Udara*, *etc.* The etiology for Ayurveda comprises *Nija (intrinsic)* and *Agantu* (extrinsic) factors which causes derangement of *Tridosha* equilibrium resulting in proliferation of cancer. This further leads to excessive metabolic crisis giving rise to malignancy [17].

Modern cancer therapy carries a great burden of chemotherapeutic drugs-induced toxic side effects, that's why absolute cure solutions of disease are sought from the traditional medicine system. About Ayurveda, the therapeutic approach is diverged into four categories as *Prakriti sthapan chikitsa* (health maintenance), *Rasayanachikitsa* (restoration of normal function by rejuvenation), *Roganashanchikitsa* (curative) and *Naishthikichikitsa* (spiritual approach). Ayurveda advocacy consisting of appropriate *Aushadh* (medicine/drug therapy), adequate *Ahara* (diet), and *Achara* (behavioural therapy including counselling) can facilitate in management of malignant conditions. The commonly reported and utilized Ayurvedic herbal decoctions comprise multiple herbs and hence possess a great perspective for a cancer cure; scientifically, these formulations act on multiple biochemical pathways and govern several organ systems simultaneously thereby aiding body's defence mechanism and nourishment at the tissue level [18].

Mechanism of Actions of Drugs from Plant Origin: Drugs from plant origin can be widely grouped into two groups based on their mode of action.

- Cell Cycle Inhibitors
- Protein Translation Inhibitors

Cell Cycle Inhibitors: Cell cycle inhibitors can be further classified in four categories based on their targets.

Cycline-Dependent Kinase (CDK) Inhibition: Cycline-dependent kinases (CDKs) are well known for their crucial role in the progression of the cell cycle. The total number of known CDKs are 13, out of which CDK1, CDK2, CDK3and CDK4 are directly involved in cell cycle regulation, whereas the remaining 9 have a peripheral role or indirect involvement. Roscovitine (isolated from *Raphanus sativus* L.) inhibits CDK2, CDK7, and CDK9 [19]. Flavopiridol (extracted from *Dysoxylum binectariferum* Hook. f.) inhibits CDK1, CDK2, CDK4, CDK6, CDK7, and CDK9 [20] **Fig. 1, Table 1.**

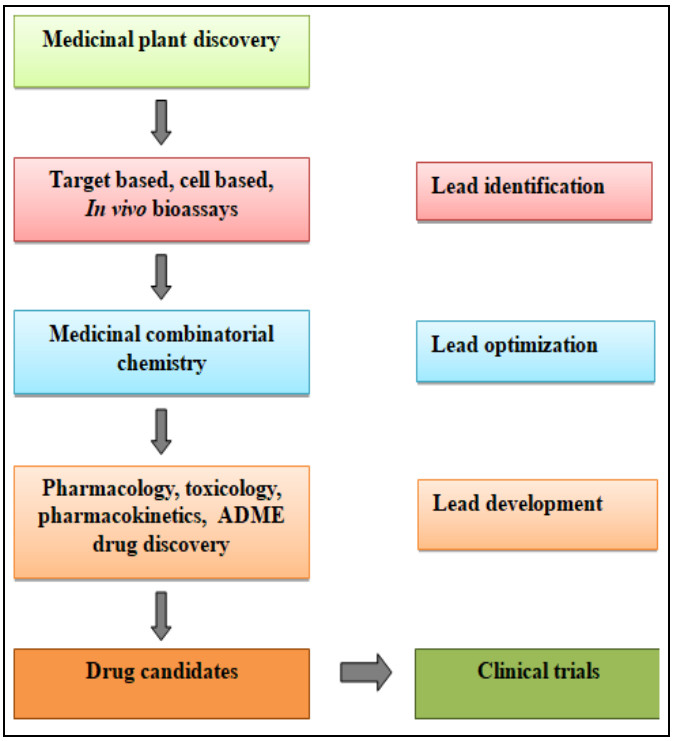

FIG. 1: SCHEMATIC OF DRUG DISCOVERY AND DEVELOPMENT FROM MEDICINAL PLANTS

TABLE 1: COMPOUNDS WITH THEIR ORIGINS, ANTI-CANCER ACTIVITY, AND THEIR CLINICAL TRIAL DEVELOPMENT HAVE BEEN REPRESENTED

Sr. no.	Name of compound	Activity	Plant source	References
1	Arglabin	Cancer chemotherapy (farnesyl transferase inhibition)	*Artemisia obtusiloba*	10
2	Betulinic acid	Anticancerous	*Betula alba*	27
3	Camptothecin	Anticancerous	*Camptotheca acuminata*	55
4	Colchiceineamide	Antitumor agent	*Colchicum autumnale L.*	56
5	Colchicine			
6	Demecolcine			
7	Etoposide	Antitumor agent	*Podophyllum peltatum L.*	57
8	Irinotecan	Anticancer, antitumor agent	*Camptotheca acuminata*	58
9	Lapachol	Anti-cancer, antitumor	*Tabebuia sp.*	59
10	Masoprocol	Cancer chemotherapy (lipoxygenaseinhibitor)	*Larrea tridentate* (Sessé & Moc. ex DC.*) Coville*	60
11	Monocrotaline	Antitumor agent (topical)	*Crotalaria sessiliforaL.*	61
12	Omacetaxinemepesuccinate (Homoharringtonine)	Oncology (protein translation inhibitor)	*Cephalotaxus harringtonia* (Knight ex Forbes) K. Koch	62
13	Paclitaxel (Taxol)	Cancer chemotherapy (mitotic inhibitor)	*Taxus brevifolia Nutt.*	63
14	Podophyllotoxin (Epipodophyllotoxin-isomer)	Antitumor anticancer agent	*Podophyllum peltatum*	64
15	Solamargine	Cancer chemotherapy (apoptosis triggering)	*Solanum spp.*	65
16	Teniposide	Antitumor agent	*Podophyllum peltatum L.*	57
17	Topotecan	Antitumor, anticancer agent	*Camptotheca acuminata*	66
18	Sulphoraphane	Induces phase 2 detoxification enzymes, inhibits tumor growth, antiproliferate effects	*cruciferous vegetables Brassica*	67
19	Vinblastine	Anti-mitotic; microtubule inhibitor, pro-apoptotic properties and induce cell cycle arrest; anti-tumour activity	*Catharanthus roseus G. Don; Vinca alkaloids*	68
20	Vincristine			
21	Vinorelbine			
22	Vindesine			
23	Vinflunine			
24	Pomiferin	Pro-apoptotic effects, inhibits cytotoxicity of cancer cells	*Maclura pomifera; Dereeis Malaccensis*	69
25	Epigallacotechin-3-gallate	anti-proliferative effects; inhibition of specific kinases; inhibit carcinogenesis	*green tea*	70, 71
26	Combretastatin A-4 phosphate	Anti-angiogenic; vasuclar shut-down of tumors; tumor necrosis	*Combretum caffrum*	72
27	Roscovitine	Inhibition of cyclin dependent kinases; reduction of cell cycle progression	*Raphanus sativus L.*	73
28	Flavopiridol	Anti-inflammatory; immunamodulatory activity	*Dysoxylum binectariferum Hook. f.*	74
29	Noscapine	Antiproliferative, inhibits tumour growth and progression	*Papaver somniferum*	75

Microtubule Inhibitors: Microtubules are tubular polymers of tubulin (single tubulin is dimer of α- and β-tubulin subunits); are highly effective and will frequently expand and contract at a rapid but constant rate.

Microtubules are necessary for cytoskeleton production, intercellular movement, cell movement, and formation of the mitotic spindle used in chromosome segregation and cellular division. Inhibition of microtubule function leads to permanent cell cycle progression disruption and to programmed cell death or apoptosis. The inhibition of microtubule is achieved either at the polymerization stage of GTP-bound tubulin or GDP-bound tubulin dissociation stage.

Colchicine and its derivatives (isolated from *Colchicum autumnale* L.) [20-21] Vincaalkaloids (isolated for *Catharanthus roseus* G. Don) [22], Combretastatin A-4 phosphate (isolated from *Combretum caffrum*) [23-24] and Noscapine (from

Papaver somniferum) [25] prevent polymerization, whereas Paclitaxel (from *Taxus brevifolia* Nutt.) prevents dissociation by stabilizing the structure [26] **Fig. 2, Table 1.**

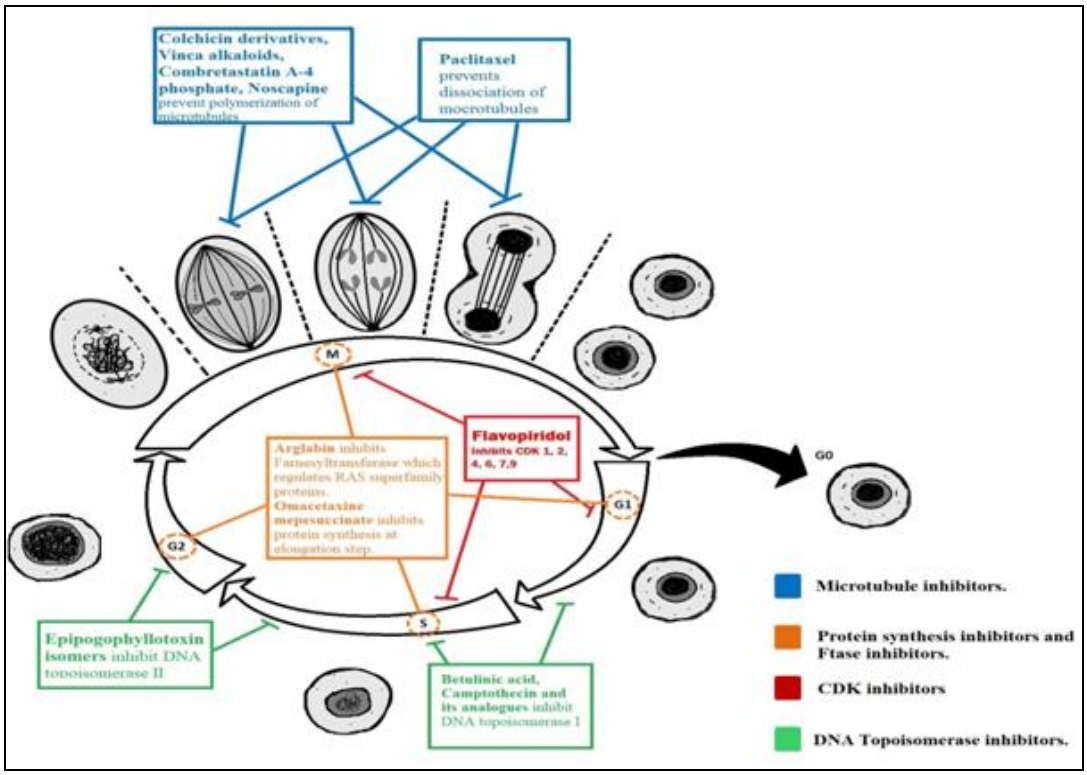

FIG. 2: MODE OF ACTION OF ANTI-CANCER COMPOUNDS

Topoisomerase Inhibition: Topoisomerases are enzymes that engage in different aspects of DNA manipulation, such as accessing DNA, removing DNA supercoils, strand breakage during recombination, chromosome condensation, and disentangling of intertwined DNA. Topoisomerase inhibitors can be grouped according to the enzyme type on which they act, *i.e.*, 1] Topoisomerase I inhibitors and 2] Topoisomerase II inhibitors.

DNA Topoisomerase I Inhibitor: Topoisomerase I inhibitors induce single-strand breaks into DNA and can work by a variety of methods, such as inhibiting the dissociation of topoisomerase and DNA, followed by replication-mediated DNA damage, that can be restored more competently in healthy cells than in cancer cells (which are deficient in DNA repair machinery).

Topoisomerase I inhibitors also give rise to gene inactivation through chromatid aberrations. Betulinic acid (isolated from *Betula alba*) (Fulda, 2008) [26], Camptothecin and its analogues i.e. Irinotecan and Topotecan (isolater form *Camptotheca acuminata*) are known to inhibit topoisomerase [27-28] **Fig. 2, Table 1.**

DNA Topoisomerase II Inhibitor: Topoisomerase II inhibitors are dominant inducers of double-strand breaks in DNA and can cause seize in the cell cycle at the G2 stage; this is achieved by deranging the interaction between topoisomerase II and cell cycle regulators, such as Cdc2. Topoisomerase II inhibitors cause a vast range of chromosomal aberrations by interfering with enzyme's catalytic activity or stabilizing easily cleavable topoisomerase II-DNA complexes; both result in double-strand breaks in the DNA. Epipodophyllotoxin-isomer *i.e.* Etoposide, Teniposide and Podophyllotoxin (isolated from *Podophyllum peltatum* L.) are well-known topoisomerase II inhibitors that arrest cell during late S and early G2 stage [29, 30] **Fig. 2, Table 1.**

Farnesyltransferase (FTase) Inhibition: The FTase is one of the three enzymes in prenyltransferase group. It attaches a 15-carbon isoprenoid called a farnesyl group to proteins possessing a CaaX motif: a four-amino acid sequence at the carboxyl terminus of a protein. FTase's targets are members of the RAS superfamily of small GTP-binding proteins pivotal

to cell cycle progression. Arglabin present in *Artemisia glabella* acts on FTase [31] **Fig. 2, Table 1.**

Protein Translation Inhibitors: Omacetaxine mepesuccinate [isolated from *Cephalotaxus harringtonii* (Forbes) K. Koch] is a protein translation inhibitor. It acts at the initial elongation step of protein synthesis; it interacts with the ribosomal A-site and prevents the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs. Omacetaxine mepesuccinate usually acts only on the initial step of protein translation[32], whereas protein synthesis from mRNAs that have already commenced translation remains unaltered **Fig. 2, Table 1.**

Nature as a Source of Therapeutic Compounds: About 40% of medicines in practice today are either natural products or semisynthetic derivatives. Natural products research explores numerous lead structures to use as templates for the development of new drugs by the pharmaceutical industry [33] **Fig. 1**. The approved lead structures represent very wide chemical diversity; they demonstrate the importance of compounds from natural sources in modern drug discovery efforts [34] **Fig. 1**. Natural products containing structural diversity have been the major resources of bioactive agents and will assist for discovering new drugs in future as well [35]. A natural product is a chemical entity produced by a living organism that has a pharmacological or biological activity for use in drug discovery and drug design. It may be extracted from tissues of plants, marine organisms, and microorganism fermentation broths. A crude extract contains novel and structurally diverse chemical compounds. The isolates from natural products often work differently than the original natural products which may have synergies.

The Natural Products - Compounds of Choicein Drug Discovery: More than 45% of today's best-selling drugs are derived from natural products or their derivatives. The biosynthesis of natural products involves repeated interactions with modulating enzymes. The biological function of many natural products can be attributed to protein target binding. Many natural products with known targets exhibit enhanced binding characteristics compared with synthetics. Since secondary metabolites from natural sources have been elaborately used within living systems since ages, they are often perceived as showing more "drug-likeness and biological friendliness (Generally Regarded As Safe- GRAS) than totally synthetic molecules", making them good candidates for further drug development [34].

Chemical Diversity of Natural Products: Bioprospecting -Chemical diversity in nature is based on diversity at both biological and geographical level, so researchers travel around the world to obtain samples to analyze and evaluate efficacy using screens or bioassays. Most biologically active natural product compounds are secondary metabolites with very complex structures. Natural products differ significantly from synthetic drugs in three important aspects, (a) in the ratio of aromatic ring atoms to total heavy atoms (lower in natural products), (b) in a number of solvated hydrogen-bond donors and acceptors (higher in natural products) and(c) natural product possess greater molecular rigidity [36].

The popularity of synthetic products has increased because of production cost, time, effectiveness, easy quality control, stringent regulation, and quick effects associated with it. However, their safety (regarding undesired effects) is questionable and cannot be overlooked. This has resulted in an increased dependence on natural products, owing to their time-tested safety and efficacy. Thus, more than 80% of the total population in the developing world relies on natural products [37].

Around 70,000 plant species have been screened for their medicinal use. Plants with ethnopharmacological applications are the primary source of medicine for early drug discovery. Fabrican and Farnsworth reported that 80% of 122 plant-derived drugs were related to their original ethnopharmacological purposes [38] **Fig. 1**. The first commercial, a pure natural product introduced for therapeutic use is morphine that Merck marketed in the year 1826 and the first semisynthetic pure drug aspirin, based on natural product salicin that was isolated from *Salix alba*, was introduced by Bayer in 1899. This led to the isolation of various early drugs, cocaine, codeine, digitoxin, quinine, and pilocarpine. Some of these are still in use, and with several recent additions which have undergone clinical trials and have been marketed as drugs

which include Paclitaxel from *Taxus brevifolia* for lung, ovarian and breast cancer, Artemisinin from traditional Chinese plant *Artemisia annua* to combat multidrug-resistant malaria, Silymarin extracted from the seeds of *Silybum marianum* for the treatment of liver diseases [39].

Antitumor Agents Novel Plant Cytotoxic Antitumor Principles and Analogs: Since, 1961, nine plant-derived compounds have been approved for use as anti-cancer drugs in the US; these are etoposide (VP-16, 1), irinotecan (Camptosar), navelbine (Vinorelbine), teniposide (VM-26, 2), taxol (paclitaxel), taxotere (Docetaxel), topotecan (Hycamtin), vinblastine (marketed as Velban) and vincristine (Oncovin). The scientific and research interest is giving great weightage to naturally derived compounds as they are considered to have less toxic side effects compared to current treatments such as chemotherapy. The Plant Kingdom produces various secondary metabolites, which are being investigated for their anti-cancer activities leading to the development of new clinical drugs. New technologies, including use of nanoparticles innano-medicines aims to enhance anti-cancer activities of plant-derived drugs by controlling the release of the compound and investigating new methods for administration.

Plant Compounds with Anticancer Properties: Many African and Asian nations still rely on plant-based treatment as their main source of medicine, and developing nations are utilizing the benefits of naturally sourced compounds for therapeutic purposes [37]. Some compounds identified and extracted from terrestrial plants for their anti-cancer properties are polyphenols, brassinosteroids, and taxols.

Polyphenols: Polyphenolic compounds include flavonoids, tannins, curcumin, resveratrol, and gallacatechins. Polyphenols have apoptosis-inducing anti-cancer properties, which can be utilized. They also can interfere with or promote the activities of cancer cell proteins. Cancer agents get altered usually through polyphenol-regulated acetylation, methylation, or phosphorylation by direct bonding.

Flavonoids: They are polyphenolic compounds and constitute a large family of about 10,000 plant secondary metabolites with known structures [40]. They are physiologically active agents in plants and are becoming compounds of high interest for their health benefits [41, 42]. There is a high content of anthocyanins, flavones, flavonols, chalcones, and many more flavonoid compounds found in just single plant parts such as its seed [43].

Brassinosteroids: Brassinosteroids (BRs) are naturally occurring herbal compounds that play roles in hormone signalling to regulate the growth and differentiation of cells.

Plant-Derived Anticancer Drugs: Plant-derived drugs can fall under four classes per their activities; methyltransferase inhibitors, DNA damage preventive drugs or antioxidants, histone deacetylases (HDAC) inhibitors, and mitotic disruptors [44]. Derivatives of vinca alkaloids such as vincristine, vinblastine, vinorelbine, vindesine, and vinflunine have been used as drugs that will inhibit the dynamics of microtubules by binding to β-tubulin. Combinations of drugs derived from vinca alkaloids, *Taxus diterpenes*, *Podiphyllum lignans* and Camptotheca alkaloids in plant extracts may enhance their anti-cancer effects and improve their efficacy as therapeutic agents [45]. The investigation on the effects of extracts from *Urtica membranaceae*, *Artemesia monosperma*, and *Origanum dayi* poston a wide range of cancer cell lines from lung, breast, colon, and prostate cancers showed that plant extracts with a combination of anti-cancer compounds were able to have a killing activity which was specific to cancer cells and showed no effect on normal human lymphocytes and fibroblasts. This makes plant extracts more desirable as therapeutic agents than chemically derived ones, which cause toxic complications in cancer treatment [46, 47]. The approved plant-derived anti-tumour compounds are Vinblastine (Velban), Vincristine (Oncovin), Etoposide, Teniposide, Taxol (paclitaxel), Navelbine (Vinorelbine), Taxotere (Docetaxel), Camptothecin (Camptosar, Campto), Topotecan (Hycamtin) and Irinotecan.

Alkaloids: *Catharanthus roseus* Vinca monoterpene indole alkaloids, such as Vinblastine and Vincristine are well known.

Etoposide and Teniposide: These two compounds were derived as semisynthetic derivatives of

podophyllotoxin, an antimitotic metabolite of the roots of the may apple plant, *Podophyllum peltatam* [48, 49], a traditional herbal remedy. Etoposide is a topoisomerase II inhibitor. This essential enzyme is involved in eukaryotic cell growth by regulating levels of DNA supercoiling [50]. Etoposide was approved as a drug for ovarian and testicular cancer, lymphoma, lung cancer, choriocarcinoma, and acute myeloid leukaemia. Teniposide was approved for malignant lymphoma, bladder cancer and central nervous system tumors.

Other compounds: The naphthoquinone pigment shikonin, a known herbal remedy, is produced by cell culturing the plant *Lithospermum erythrorhizon*, mainly for its use in cosmetics. Unexpectedly, shikonin and two derivatives were found to inhibit tumour growth in mice bearing Lewis Lung Carcinoma [51]. Other natural products include the isoflavonegenistine, indole-3-carbinol (I3C), 3, 3′-diindolemethane, and curcumin(-)-epigallocatechin-3-gallate, resveratrol and lycopene are known to inhibit the growth of cancer cells [52]. These natural compounds appear to act by interfering multiple cellular signalling pathways, activating cell death signals and bringing on apoptosis of cancer cells without negatively affecting normal cells.

Plants Possessing Promising Anticancer Potential: Large numbers of plants have already been screed as discussed earlier, but nature has always more to offer. A number of scientific reports suggest that various plants such as *Allium sativum, Amorphopallus campanulatus, Andrographis paniculata, Annona atemoya, Baliospermum montanum, Barleria prionitis, Basella rubra, Calotropis gigantean, Curcuma domestica, Datura metel, Ficus benghalensis, Flacourtia indica, Hygrophilaauriculata, Juniperusindica, Madhuca indica, Moringa oleifera, Nigella sativa, Oxoxylum indicum, Pandanus odorifer, Phyllanthus niruri, Picrorrhiza kurroa, Piper longum, Podophyllum hexandrum, Prosopis cineraria, Pterospermum acerifolium, Raphanus sativus, Rubiac ordifolia, Semecarpus anacardium, Tinospora cordifolia* and *Vitis vinifera* possess promising anti-cancer property [16]. These plants can be thoroughly studied, and their anti-cancer property can be evaluated, and harnessed for better treatment. Further, these combinatorial chemistry techniques can be used in unveiling the mechanisms of many formulations of Ayurveda in various dosage forms. In the continuing search for potential anti-cancer agents, GL331 (a derivative of 4-Amino-etopodophyllotoxin) is currently in phase II clinical trials. The state-of-the-art technologies, such as natural product discovery, genomics, proteomics, metabolomics, metagenomics, structure-function-based drug design, semi-synthesis, recombinant DNA methodology, genome mining, and combinatorial biosynthesis have already proved their potential in drug discovery and characterization [53]. However, in the past few years, more than 100 new cytotoxic antitumor compounds and their analogues have been found with confirmed activity in the NCI using *in-vitro* human tumour cell lines bioassay. These compounds are of much interest to NCI for further in vivo evaluation and to further use for lead improvement and drug development [54]. Based on this successful identification of plant-derived antitumor drug candidates, we can look forward to future successes in this research area.

One major asset of medicinal plant-based drug discovery is Ethno pharmacological information providing hints for therapeutically effective compounds in humans. In order to harvest its full potential, adopting a broad interdisciplinary approach involving ethnopharmacological knowledge, botany, phytochemistry, and more relevant pharmacological testing strategies (e.g., early in vivo efficacy studies and compound identification strategies) metabolism and synergistic action of the plant constituents). The mining for new active compounds is a never-ending quest that has led us so far to nine plant-derived compounds that are already approved as anti-cancer drugs and a few new plant-derived compounds namely 10-hydroxycamptothecin, curcumol, curdione, d-tetrandrine, gossypol, homoharringtonine, indirubin, lycobetaine and monocrotaline that possess promising potential [17].

Still plants listed above can be future hope for obtaining new, more effective drugs.

CONCLUSION: Although comparative genomics can disclose new targets for drugs, the numbers of targets are so large that it requires tremendous time and money to set up all the screens necessary to

exploit this resource. This can only be taken care of by high-throughput screening methodology, which demands timely updated libraries of millions of chemical entities. Thus, the future success of the pharmaceutical industry depends not only on high-throughput screening and combinatorial chemistry but also imbibing complementary technologies like multi-omics. Further, natural product discovery combined with fundamental pharmacological principles of traditional medicine systems can surely give better insights and contribute to P4 medicine.

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