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Naturally Derived Formulations and Prospects towards Cancer

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Abstract

Traditional Medicine (TM) and their secondary metabolites are being increasingly recognized as useful complementary treatments toward the cancer. A large number of clinical studies have reported and proven concern of cancer patients. Here we have also reported recent studies on the biochemical and cellular mechanisms of Traditional Medicine (TM). Nowadays, Chemotherapy and surgery are standard methods for treatment of cancer, but still it's not been fully successful. Some progress has been made in cancer diagnosis and treatment, but high incidence rate of cancer and low survival rate of patient are still being reported worldwide. Since ancient times, a number of traditional medicines known as Ayurveda, Siddha, Unani, Iranian, Chinese, Korean, acupuncture, Muti, Ifa, and African medicine are widely used for therapeutic purposes and are becoming popular as Traditional Medicine (TM). It has been reported that plants synthesize plethora of "secondary metabolites" or "phytochemicals", proven to possess anti-mutagenic and anti-cancer properties in many research studies. There are many possibilities for further organized research for screening of medicinal plants for their potential and efficacy against chronic diseases such as a cancer and other inflammatory diseases. Therefore, researcher's interest should be in identification and standardization of new anti-cancer drug with low side effects and greater efficacy, that is easily acceptable in medical community and which may overcome the challenges in present and future cancer therapy. This review explores therapeutic value of certain bio-active principals of plant which could serve as potential pharmacologically active drug for treatment of cancer in future.

Keywords

Bio-Active Principles, Cancer, Chemotherapy, Phytochemicals, Secondary Metabolites

1. Introduction

1.1. Conventional Cancer Therapy

Cancer is a state which arises when cells start dividing in an uncontrolled manner disobeying the check mechanisms, which controls the rate of cell proliferation leading to the formation of a neoplastic tumor, which may be benign or malignant. Cancer arises mainly due to two reasons: one is Gain of function of a proto-oncogene, which makes it oncogenic and second is Loss of function of a tumor suppressor gene [1]. Despite the latest advancements in the cancer treatment it remains a key cause of death worldwide [2]. Current treatment includes chemotherapy, radiations and surgery, out of which chemotherapy is most common. Most successful chemotherapeutic agents include: Taxanes-paclitaxel (Taxol), docetaxel (Taxotere), albumin bound paclitaxel (Abraxane), Anthracyclines-doxorubicin, pegylated liposomal doxorubicin, epirubicin, Platinum agents-cisplastin, carboplastin etc. All these agents cause serious side effects [3] [4] [5], which includes kidney, liver, nerve and blood vessel damage, hearing loss, lower blood count etc. [6] [7], regional toxicity affecting mucosa cells, causing irritative urinary and blood loss [7]. Later toxic effects include damage to proliferating cells such as fibroblasts, endothelial and parenchymal cells [7]. Other undesired side effects such as immune suppression, bone necrosis, lung fibrosis and skin devascularization are seen with all conventional therapies [5] [6] [7] [8]. Although the desired goal of chemotherapy is to eliminate the tumor cells, diverse range of normal cells is also affected, leading to many adverse side effects on multiple organ systems [9]-[14]. Such debilitating effects and toxicity are a major clinical problem which limits the usefulness of anticancer agents [15] [16]. Knowing how the chemotherapeutic agents work is important in predicting its side effects. For instance, treatment with alkylating agents and topoisomerase II inhibitors increases the risk of secondary cancer (acute leukaemia); anthracyclines (like doxorubicin) induce cardiotoxicity; and mitotic inhibitors have the potential to cause peripheral nerve damage [17]. Over 75% of cancer patients suffer from therapy associated fatigue, nausea, vomiting, pain, rashes, infection, headaches, which considerably decreases the quality life of the patients [3] [13] [15] [18] [19]. They also affect the nutritional status of the patients [3] [18] causing malnutrition, which is one of the major reasons why cancer patients die [6] [18]. Ongoing researches on several secondary metabolites are under clinical trials for the treatment of various diseases including cancer. TM/CAM and its derived compounds are an essential aspect for therapeutics, and nano-particles based approaches could be a new hope for additional therapy for cancer treatment [20].

1.2. Ancient History of Traditional Medicine

From ancient times, traditional medicinal plants are being used for treatment of various diseases [21]. Natural medicine sometimes referred to as herbalism or botanical medicine is the use of plants for their therapeutic or medicinal value

and has been used by many cultures throughout history [22]. The oldest written facts about medicinal plants and the uses of plants are contained in thousands of poetic hymns in the Rig Veda. The first school to teach Ayurvedic medicine was at the University of Banaras in 500 BC where the great Samhita (or encyclopedia of medicine) was written. Another great enclyclopedia was written 700 years later, and these two together forms the basis of the Ayurveda or Indian medicinal plant concept [23]. The different indigenous system of medicine namely Ayurveda, Siddha, Unani, Iranian, Chinese, Korean, acupuncture, Muti, Ifa, and African medicine have been in existence and used in several countries for treatment. These systems of medicine provide to the needs of nearly 70% of the population residing in the villages. Apart from India, these systems of medicine are prevalent in China, Korea, Middle Eastern, European, Africa and America and many other countries [24] [25]. India has a rich culture of using medicinal herbs and spices, which includes about more than 2000 species and has a vast geographical area with high potential abilities to be used as traditional medicines but only very few have been considered chemically and pharmacologically for their prospective medicinal value [26]. In 1819, morphine, codeine and paregoric acid were isolated which laid down the foundation for isolation of pharmacologically active compounds. Even today, morphine remains the standard for measuring synthetic analgesic drugs. In addition U.S. based research has proved the medicinal properties of alkaloids from Madagascar periwinkle (*Catharanthus roseus*), used in the chemotherapy of childhood leukemia and for the treatment of Hodgkin's disease (*Taxus brevifolia*), and approved by FDA in 1992. As per our recent knowledge about 25% to 30% of the prescribed drug contains at-least one or two active ingredients derived from plants [27]. Many drugs listed as conventional medications were originally derived from plants [28]. Salicylic acid, a precursor of aspirin, was originally derived from "white willow bark" and "meadowsweet plant" [29]. Other plant derived drugs include the anti-malarial "quinine" extracted from the bark of Cinchona species. "Vincristine" used in cancer treatment is derived from "Madagascar periwinkle" (*Catharanthus roseus*) [30].

1.3. Traditional Medicine

The use of traditional medicine (TM) and complementary and alternative medicine (CAM) as therapeutics is growing all over the world [31]. Already, it accounts for a major part of the health care provided worldwide. In low- and middle-income countries, up to 80% of the population relies on TM for their primary health care needs [32]. In many high income countries CAM utilization is becoming increasingly popular, with up to 65% of the population reported that they have used this form of medicine [32] [33]. Today plant based drugs play an essential role in health care. According to WHO, 80% of the world population rely on traditional medicines for primary health care [34]. Currently 119 chemicals derived from 90 plant species constitute major drugs. Studies showed that plant derived drugs represent about 25% of the American drug market [35].

There are more than 250,000 plant species in world with unique secondary constituents [36], however, only few of them have been investigated for their potential value as a drug. Furthermore, medicinal plants typically contain mixtures of different phytochemicals that may act individually, additively or in synergy to improve health [37] and enhance mood and give a sense of well-being [38]. Now we have enough scientific reasons for using TM/CAM as a more effective therapy in comparison to conventional medicines. Apart from therapy some Indian and African communities, traditional medicines are thought to help clean out negative spiritual influences [39] and supporters of TM/CAM use them frequently as they are generally safe at common doses [40]. More than 3000 plants based secondary metabolite worldwide have been clinically reported to have anticancer properties [41] [42]. TM/CAM medicine use is still common in oncology therapy worldwide [43] [44]. In the last two decades, the use of herbal remedies has also been widely increased in many developed countries as TM/CAM. Secondary metabolite have increasing attention in cancer chemotherapy because they are viewed as more biologically active target sites and are less toxic to normal cells [45]. Moreover, there is evidence that natural product-derived anticancer drugs have alternative modes of promoting cell death [46] [47]. In fact, the use of TM/CAM based metabolite as the background to discover and develop a drug entity is still a research attention.

1.4. WHO Traditional Medicine Strategy

According to WHO definition of traditional medicine (TM) is as follows "Diverse health practices, approaches, knowledge, beliefs incorporating plant, animal, and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness" [48]. TM is a comprehensive word used to refer many systems of traditional medicine and other various forms of local medicines.

In developed and developing countries where the dominant health care systems look forward on allopathic medicine, apart from conventional approach now scientist are thinking toward traditional medicine (TM) and these medicine often termed as "complementary' alternative" or "non-conventional" medicine. Herbal medicine includes herbs and plant active ingredients or plant secondary metabolites. In addition general sense to all above mentioned regions for Traditional Medicine/Complementary alternative medicine (TM/CAM) is still in used [48] for their healthcare purposes. In many parts of the world expenditure on TM/CAM is increasing rapidly. The mission of WHO for essential drugs and medicine policy is that: it helps to save lives and improve healthcare facilities by healing the huge gap between the potential that essential drugs have to offer towards patient care patients care. In most developing countries, national TM/CAM institutes have been established, like in India, China, North and South Korea, Ghana, Indonesia, Mali, Madagascar, Nigeria, Sri Lanka, Thailand, Viet-

nam and list goes on. In addition WHO also provides guidelines, scientific information and research grant into the safety and efficacy of use of TM/CAM.

According to WHO TM strategy, the functions of WHO in TM/CAM can be outlined as follows (WHO traditional medicine strategy: 2014-2023):

- Facilitating integration of TM/CAM into national healthcare systems by helping member states to develop their own national policies on TM/CAM.
- Producing guidelines for TM/CAM by developing and providing international standards, technical guidelines, and methodologies for research into TM/CAM therapies and products, and for use during manufacture.
- Stimulating strategic research into TM/CAM by providing support for clinical research projects on safety and efficacy of TM/CAM, particularly with references to diseases such as malaria and HIV/AIDS.
- Advocating the rational use of TM/CAM by promoting evidence based TM/CAM.
- Managing information on TM/CAM by acting as a clearing house to facilitate information exchange on TM/CAM.

1.5. Formulation Development and Discovery

Discovery of TM/CAM drugs has become one of the main areas of interest in pharmacological research [1] [45] During the last few years, the development of active compounds (plant secondary metabolites) based drugs has risen significantly, this can, in part, be attributed to the new technologies in natural product isolation and purification, combinatorial synthesis and high-throughput screening [49]. Natural products from dietary components such as Indian spices and medicinal plants are known to possess antioxidant activity. Recently, more than 100 new active compounds have been isolated as anti-cancer agents from plant sources [1]. Drug development is an essential part of research owing to low bio-availability of flavonoids and their lack of stability, excessive metabolism, permeability problems, lack of site specificity in distribution, rapid elimination etc. The scope of this review is to assess and put into perspective salient features of some recently reported work on Plant secondary metabolites including the methylated compounds that showed improved drug like properties [50]. Nowadays a number of approaches are being considered for selecting higher plants as reference for anti cancer drug development with the aim of drug accomplishment, and to highlight the role of ethno medicine [51]. During the last few decades, a wide range of anti-cancer agents were discovered from plants, but only a few of them managed to reach clinical use, from their successful chemical identification, to their effectiveness in therapeutic cancer treatment. Each of them has their advantages and limitations. Few of them approved by FDA are Vincristine [52], Paclitaxel [53] [54], Homoharringtonine [55], Curcumin [56] and Betulinic Acid [57]. All of them are derived from natural products [58].

1.6. Active Secondary Metabolites

Phytochemicals (plant secondary metabolites) are bioactive substances or active

ingredients of plants which are responsible for its biological and medicinal properties [59]. They have found to be associated in the protection of humans against chronic degenerative diseases [60]. The term "Phytochemical" according to American Cancer Society refers to a wide variety of compounds produced by plants and can be found in fruits, vegetables, beans, grains etc. The isolated active compounds from these plants are used for applied research. Some of the plant chemicals are: flavonoids, alkaloids, saponins, tannins, cardiac glycosides, antharquinones, sterols and triterpenes etc. [61].

- **Flavonoids:** Flavonoids are water soluble polyphenolic molecules containing 15 carbon atoms and is the most studied phytochemical. They can be visualized as two benzene rings which are joined together with a three carbon chain. One of the carbons of the short chain is always connected to a carbon of one of the benzene rings, either directly or through an oxygen bridge, thereby forming a third middle ring [62]. They can be classified into six major sub-groups: flavones, flavonols, flavanones, catechins, anthocyanidins and isoflavones [63]. Quercetin, is one of the best described of this group. It is found in abundance in onions, apples, broccoli and berries. Flavonoid is involved in the scavenging of oxygen derived free radicals [63], and is also a potent hypolipidemic agent [64]. They possess a high antioxidant potential due to their hydroxyl groups and protect efficiently against diseases like arteriosclerosis [65] [66]. Experimental studies showed that flavonoids enhance vaso-relaxant process [67] and prevent platelet related thrombosis [68].
- **Saponins:** They are naturally occurring surface glycosides. They are synthesized by plants, some bacteria and lower marine animals [69]. Saponins derived its name from its ability to form soap like foams in aqueous solutions [70]. The structure of saponin consists of a sugar moiety (glucose, galactose, glucuronic acid, xylose, rhamnose or methyl pentose) which is linked via glycosidic linkage and attached to a hydrophobic aglycone (sapogenin) which may be a triterpenoid or a steroid. Two types of saponin have been identified, the triterpenoid and steroid saponins. The steroid saponins are often found in medicinal plants, oats, capsicum, pepper, aubergine and ginseng. Triterpenenoid saponins can be found in many legumes such as soyabeans, beans, peas, lurcene etc. [71]. Both triterpene and steroidal aglycones have a number of different substituents (H, COOH, and CH_3). The sugars can be attached to the aglycone either as one, two or three side chains [72]. Saponin exhibits anti-microbial activity and has a lytic effect on erythrocyte membrane [73]. It has also demonstrated hypoglycemic effect [74] and lowering of serum cholesterol levels in animals [75] [76]. Saponins reduce protein digestibility by the formation of sparingly digestible saponin-protein complexes [77]. Endogenous saponins affects the chymotrypsic hydrolysis of soyabean protein, particularly glycinin [78]. Saponins have been reported to be highly toxic to fish because of their damaging effect on the respiratory epithelia [79]. They are also considered to be the active compo-

nents of many traditionally used fish poisons, like mahua oil cake [80]. Quin and Xu found that the butanol extract of *Mussaenda pubescens* was capable of terminating pregnancy in rats [81]. Saponins exhibit abortifacient, anti-zygotic and anti-implantation properties and are often used as contraceptives in many places [73]. Saponin isolates have also shown specific inhibition on the growth of cancer cell in vitro [82], and anti-oxidant properties [83].

- **Alkaloids:** Alkaloids are a group of complex nitrogen containing compounds derived from microbes, marine organisms and plants. Alkaloids are structurally diverse with over 12,000 structures elucidated from plants [84] [85] [86]. Well known alkaloid compounds include-purine alkaloids (caffeine, theobromine), tropane alkaloids (cocaine, scopolamine), benzyl isoquinoline alkaloids (berberine, morphine) and monoterpenol indole alkaloids (vinblastine, ajmaline). Alkaloids are classified based on their primary metabolite purine alkaloids that are produced from adenine or guanine. Tropane alkaloids (TA) are produced from ornithine, Isoquinoline alakloids (IQA) are produced from tyrosine, Monoterpenoid indole alkaloids (MIA) derived from tryptophan [87]. They are used widely as anti-cancer agents, anti-malarials and analgesic and in the treatment of Parkinson's hypertension and central nervous system disorders [88].
- **Tannins:** Tannins (tannic acids) are naturally occurring complex chemicals found in plants. They are of two distinct types: Hydrolysable tannins (polyesters of gallic acid) and Condensed tannins [89]. Hydrolysable tannins are gallic acid and egallic acid that consist of polyols such as sugars and phenolics such as Catechin. P-Penta-O-galloyl-D-glucose is tannic acid and is the model compound for this group of tannins. Hydrolysable tannins are further classified according to the products of hydrolysis; gallotannins yield gallic acid and glucose, and ellagitannins yield ellagic acid and glucose [90]. Condensed tannins include Pro-anthocyanidins that are polymers of flavan 3-ols linked through an interflavan carbon bond. Thus more accurate definitions are needed and the most unambiguous tannin definition is based on their chemical structures. In addition to their fundamental activities, *i.e.*, binding to proteins, large molecular compounds and metallic ions, and also exhibiting antioxidant activities. Some structure-specific activities were found for the condensation of dehydroellagitannins with co-existing compounds under mild conditions, and the host-mediated antitumor actions of ellagitannin oligomers [91] [92].
- **Cardiac glycosides:** The aglycone part of cardiac glycosides is a tetracyclic steroid with an attached unsaturated lactone ring that may have 5 or 6 members. Cardiac glycosides are classified into two groups according to the lactone ring: the C-23 cardenolides with an α,β-unsaturated δ-γ-lactone (butenolide) and the C-24 bufadienolides with a di-unsaturated γ-lactone (pentadienolide). Majority of saccharides found in cardiac glycosides are highly specific. They are 2,6dideoxyhexoses, such as D-digitoxose, L-oleandrose or D-diginose.

Cardiac glycosides such as digitoxin from Digitalis have been used as drugs for the treatment of cardiac insufficiency. Apart from that cardiac glycosides are also being used in the treatment of cancer. These compounds typically inhibit cancer cell proliferation and growth and activate tumor-specific immune responses. They are ligands for Na/K-ATPase, which is a promising drug target in cancer [93] [94] [95].

1.7. Traditional Medicine and Anti-Cancer Properties

Cancer is a major global health burden with approx 10.9 million new cases, 6.7 million deaths and 24.6 million surviving patients all around the world since 2002 [96] [97]. Since 1990, there has been 22% increase in cancer cases and mortality, with most frequent cancers being lung, breast, colorectal, stomach, oral, skin and ovary [98] [99].

Thus it has become necessary to investigate new strategies to prevent and treat cancer. Medicinal plant derivatives and secondary metabolites have played important roles in the treatment of cancer. The National Cancer Institute has collected about 35,000 plant samples from 20 countries and screened out 114,000 extracts for anti-cancer activity [97]. Of all the available anti-cancer drugs during 1940-2002, 40% were natural products or their derivatives, another 8% were natural products mimics [100]. Anti-cancer agents from medicinal plants that are currently in use can be grouped into four classes of compounds: Vinca (or Catharanthus) alkaloids, epipodophyllotoxins, taxanes and camptothecins. Vinblastine and vincristine are isolated from *Catharanthus roseus* and have been clinically used for over 40 years [101], for a variety of cancers including leukemia, lymphomas, advanced testicular cancer, breast and lung cancers and Kaposi's sarcoma [100]. The mechanism of action of vinca alkaloids and several other semi-synthetic derivatives is blocking mitosis with metaphase arrest, which occurs by binding specifically to tubulin resulting in its depolymerization [102]. Podophyllotoxin isolated from resin of *Podophyllum peltatum* was found to be too toxic to host so its derivatives were made [103]. Etoposide and teniposide are two semi-synthetic derivatives of epipodophyllotoxin and are used in the treatment of lymphomas, bronchial and testicular cancers [100] [102] [103] [104]. The epipodophyllotoxin binds tubulin, causing DNA strand breaks during the G2 phase of the cell cycle by irreversibly inhibiting DNA topoisomerase II [103]. Paclitaxel was isolated from *Taxus brevifolia* and is significantly active against ovarian cancer, advanced breast cancer, small and non-small cell lung cancer [105] [106] [107]. The taxanes including Paclitaxel and its derivatives act by binding to tubulin without allowing depolymerization or interfering with tubulin assembly [108] [109]. The cells show defects in mitotic spindle assembly, chromosome segregation, and cell division and are unable to achieve metaphase spindle configuration. The spindle inhibition role is attributed to suppress the microtubules dynamics and occurs at lower concentrations than those needed to block mitosis. Camptothecin isolated from *Camptotheca acuminata*, originally showed unacceptable myelosuppression [105]-[112]. However, interest in

Camptothecin revived when it was found to be selective inhibitor of topoisomerase I, involved in cleavage and reassembly of DNA [112]. The effect causes damage in DNA and apoptosis of the cancer cells due to the conversion of single-strand break into double-strand break resulting from the collision of the replication fork at cleavable complex. Together taxanes and camptothecins account for approximately one third of the global anti-cancer market in 2002. Numerous derivatives of all four compound classes are currently in clinical use. There are more than 270,000 plants existing on this planet waiting to be explored [113]. Here we have also mentioned some of plant active principles and there activity on different cancer cell lines with structural formulas in **Table 1**.

1.8. TM/CAM Safety Features

Secondary metabolites are in great demand due to their inexpensiveness, better cultural acceptability, and better compatibility with minimal side effects [159]. They are relatively safe because they are derived from natural compounds rendering less toxicity [160]. They are also potential source of chemical constituents with anti-tumor and cytotoxic activities [161] [162]. They have anti-cancerous potential due to occurrence of natural antioxidants acting as reducing agents, free radical scavengers and quenchers of singlet oxygen. Greater part of their antioxidant action is due to bioactive compounds viz flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignans, catechins and isocatechins that help in reducing or minimizing the toxic side effect of conventional treatments [12] [163].

2. Limitations

The traditional medicine takes long time to act and gives response towards the disease in slow manner. The active principles of medicinal plants are also allergic sometimes. Herbal medicines are not effective in case of cancer, chronic diseases, and sudden illness and auto immune diseases. Herbal medicines isolation and characterization for the drug discovery have numerous limitations, if incorrect identification is done it can lead to serious side effects. It is generally observed that herbal medicines are not properly regulated because it has so many secondary metabolites such that it does not show quality assurance. While using active plant derived secondary metabolites having obstacles toward the cancer and other chronic diseases: Plant active secondary metabolites may vary regions to region according to geographical with lack of definite safety consideration behalf of specificity and sensitivity because its highly complex active personalized ingredient for specific formulations in addition one of the major drawbacks of the plant metabolite is lack of defined molecular targets.

3. Future Prospects and Applications

In the future, each patient should have their own unique chemotherapy protocol, which improves the therapeutic quality by selecting and prescribing

Table 1. In vitro effects of various bioactive compounds: mechanism, structure on various cancer cell line.

Cancer type	Active Compound and Structural Formula		Mechanism of action	Cell lines	References
Breast cancer	FLAVONOIDS	Flavanones ($C_{15}H_{10}O_3$) Daidzein ($C_{15}H_{10}O_4$) Genistein ($C_{15}H_{10}O_5$) Quercetin ($C_{15}H_{10}O_7$) Luteolin ($C_{15}H_{10}O_6$)	Inhibition of the Epidermal Growth Factor (EGF) receptor in the sub-micromolar range by competing with ATP for its binding site.	MCF-7	[114] [115]
	ALKALOIDS	Vinblastin ($C_{46}H_{58}N_4O_9$) Vincristine ($C_{46}H_{56}N_4O_{10}$) Taxol ($C_{47}H_{51}NO_{14}$) Noscapine ($C_{22}H_{23}NO_7$)	Cellular microtubules stabilization by binding to β-tubulin subunit, causing interference in their normal breakdown during cell division, with resultant stabilization of the polymer through protection from disassembly.	MDA-MB-231 MCF-7	[116] [117] [118] [119]
	SAPONINS	Saponins ($C_{44}H_{70}O_{17}$)	Induce cell cycle (G1) arrest, Apoptotic and anti-proliferative activity.	MDA-MB-453, MCF-7	[120] [121]
	TANNINS	Maplexins A ($C_{13}H_{16}O_9$)	Inhibition of cellular proliferation.	MCF-7, MCF7/HER2, JIMT-1	[122] [123]
	CARDIAC GLYCOSIDES	Digitoxin ($C_{41}H_{64}O_{13}$) Digoxin ($C_{41}H_{64}O_{14}$) Proscillaridin ($C_{30}H_{42}O_8$) Ouabain ($C_{29}H_{44}O_{12}$)	Inhibition of Topoisomerases I and II.	MCF-7, MDA-MD-435	[124] [125]
Leukemia	FLAVONOIDS	Sophoranone ($C_{30}H_{36}O_4$) Genistein ($C_{15}H_{10}O_5$) Apigenin ($C_{15}H_{10}O_5$) Quercetin ($C_{15}H_{10}O_7$) Myricetin ($C_{15}H_{10}O_8$) Chalcones ($C_{15}H_{12}O$)	Inhibition of cell growth Induction of apoptosis. Induction of phase II metabolizing enzymes such as glutathione-S-transferase, quinine reductase, and UDP-glucuronyltransferase resulting in detoxification and elimination of carcinogens from the body.	U937 cells,HL-60, K562, Jurkat	[126] [127] [128] [129]

Continued

	ALKALOIDS	Vinblastin ($C_{46}H_{58}N_4O_9$) Vincristine ($C_{46}H_{56}N_4O_{10}$) Cryptolepine ($C_{16}H_{12}N_2$)	Inhibition of cellular proliferation by altering the dynamics of tubulin addition and loss at the ends of mitotic spindle microtubules.	CCRF-CEM CEM/VM-1	[119] [130] [131] [132]
	SAPONINS	Saponin ($C_{44}H_{70}O_{17}$)	Causes cytotoxicity and apoptosis in tumor cells.	Jurkat, HL 60	[120] [133]
	CARDIAC GLYCOSIDES	Bufalin ($C_{24}H_{34}O_4$) Oleandrin ($C_{32}H_{48}O_9$) Digitoxin ($C_{41}H_{64}O_{13}$) Proscillaridin A ($C_{30}H_{42}O_8$) Ouabain ($C_{29}H_{44}O_{12}$)	Inhibition of topoisomerases I and II, Increased activation of MAPKs, Down regulation of cyclin A, Bcl-2 and BclxL, Increased expression of p21 and Bax.	HL60, U-937, CCRF-CEM, CEM-VM-1	[125] [134] [135]
Stomach	FLAVONOIDS	Sophoranone ($C_{30}H_{36}O_4$)	Inhibition of cellular growth and induction of apoptosis. Inhibition, reversion or retardation of cellular hyperproliferation.	MKN7 cells	[136]
	SAPONINS	Saponins ($C_{44}H_{70}O_{17}$)	Cytotoxic effects on tumor cells.	SGC-7901	[137]
Colon Cancer	FLAVONOIDS	Flavone ($C_{15}H_{10}O_2$) Quercetin ($C_{15}H_{10}O_7$) Genistein ($C_{15}H_{10}O_5$) Anthocyanin ($C_{15}H_{11}O+$)	Inhibition of cellular proliferation and cytotoxicity, Perturbations in cell cycle progression. Checkpoints at both G1/S and G2/M of the cell cycle.	Caco-2 and HT-29	[138] [139] [140]
	ALKALOIDS	Camptothecin ($C_{20}H_{16}N_2O_4$) Topotecan ($C_{23}H_{23}N_3O_5$) Irinotecan ($C_{33}H_{38}N_4O_6$) Arctigenin ($C_{21}H_{24}O_6$)	It involves binding topoisomerase I–DNA covalent complex, forming a ternary complex that gets stabilized and DNA is prevented from religation during replication, that leads to damage in DNA and apoptosis of the cancer cells as single-strand break converts into double-strand break	CaCo2, T84	[141] [142] [143] [144]
	SAPONINS	Saponins ($C_{44}H_{70}O_{17}$)	Inhibits cell proliferation through accumulation in S phase and G2/M arrest, with concomitant suppression of p21 expression and inhibition of cyclin-dependent kinase activity.	HT-29, C26	[145] [146]

Continued

	TANNINS	Maplexins A –I ($C_{13}H_{16}O_9$)	Down-regulation of cyclins A and B1 and upregulating of cyclin E, cell-cycle arrest in S phase, induction of apoptosis via intrinsic pathway (FAS-independent, caspase 8-independent) through bcl-XL down-regulation with mitochondrial release of cytochrome c into the cytosol, activation of initiator caspase 9 and effector caspase-3.	HCT-116, Caco-2, CCD-112CoN	[147] [148]
Oral Cancer	FLAVONOIDS	Flavanones ($C_{15}H_{10}O_3$) Isoflavonone ($C_{15}H_{12}O_2$) EGC ($C_{15}H_{14}O_7$) Chalcones ($C_{15}H_{12}O$) EGCG ($C_{22}H_{18}O_{11}$) Curcumin ($C_{21}H_{20}O_6$) Genistein ($C_{15}H_{10}O_5$) Quercetin, ($C_{15}H_{10}O_7$) Cisplatin ($C_{20}H_{28}N_{12}O_9PPt+$)	Interaction with phase I metabolizing enzymes (e.g., cytochrome P450), which metabolically inactivate a large number of procarcinogens.	HSC-2, HSG, SCC-25	[149] [150] [151] [152] [153]
	TANNINS	Total Pomegranate Tannin (TPT) extract	Anti-proliferative activity	KB, CAL27	[147]
Lung Cancer	FLAVONOID	Flavone ($C_{15}H_{10}O_2$) Quercetin ($C_{15}H_{10}O_7$)	Inhibition of tyrosine kinases.	SK-LU1, SW900, H441, H661, haGo-K-1, A549	[154] [155]
	ALKALOID	Vinblastin ($C_{46}H_{58}N_4O_9$) Vincristine ($C_{46}H_{56}N_4O_{10}$) Taxol ($C_{47}H_{51}NO_{14}$) Camptothecin ($C_{20}H_{16}N_2O_4$)	Inhibition of cellular proliferation by altering the dynamics of tubulin addition and loss at the ends of mitotic spindle microtubules.	A549	[117] [119] [141] [156] [157]

Continued

	Sanguinarine ($C_{20}H_{14}NO_4$) Chelerythrine ($C_{21}H_{18}NO_4$)			
	Chelidonine ($C_{20}H_{19}NO_5$) Noscapine ($C_{22}H_{23}NO_7$)			
SAPONINS	Saponins ($C_{44}H_{70}O_{17}$)	Apoptosis, cytotoxic activity.	A549, NCI-H727	[133] [137]
CARDIAC GLYCOSIDES	Digitoxin ($C_{41}H_{64}O_{13}$) Digoxin ($C_{41}H_{64}O_{14}$) Ouabain ($C_{29}H_{44}O_{12}$) Oleandrin ($C_{22}H_{23}NO_7$)	Initiates Apo2L/TRAIL apoptosis via increased expression of death receptors 4 and 5	NCI-H-358, Calu1, Sklu1, NCI-H6, H69AR	[158]

well-matched drugs and avoiding ineffective ones [58] [164]. Applying such individualized chemotherapeutics through a personalized chemotherapy regime will further improve the final outcome [18] [165]. This will be accompanied by the identification and testing of novel, more specific and selective drugs either via synthetic routes or by purifying from herbal sources [166]. Although the novel chemotherapeutic agents will be more and more effective against the tumor cells, their toxicity to normal tissues as well as drug resistance remains the major obstacle for clinical use [167]. Personalized approach using various phytochemical compounds provides a new dimension to the standard cancer therapy for improving its outcome in a complex and complementary way [168] (**Figure 1**).

Medicinal plants are also important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds [169] [170]. Major pharmaceutical companies are presently conducting extensive research on plant materials gathered from various habitats for their potential medicinal value [171]. Rather than using whole plant, scientists identify, isolate, extract and synthesize individual active compounds. Because modern pharmacology looks for one active ingredient and seeks to isolate it to the segregation of all the others, most of the research

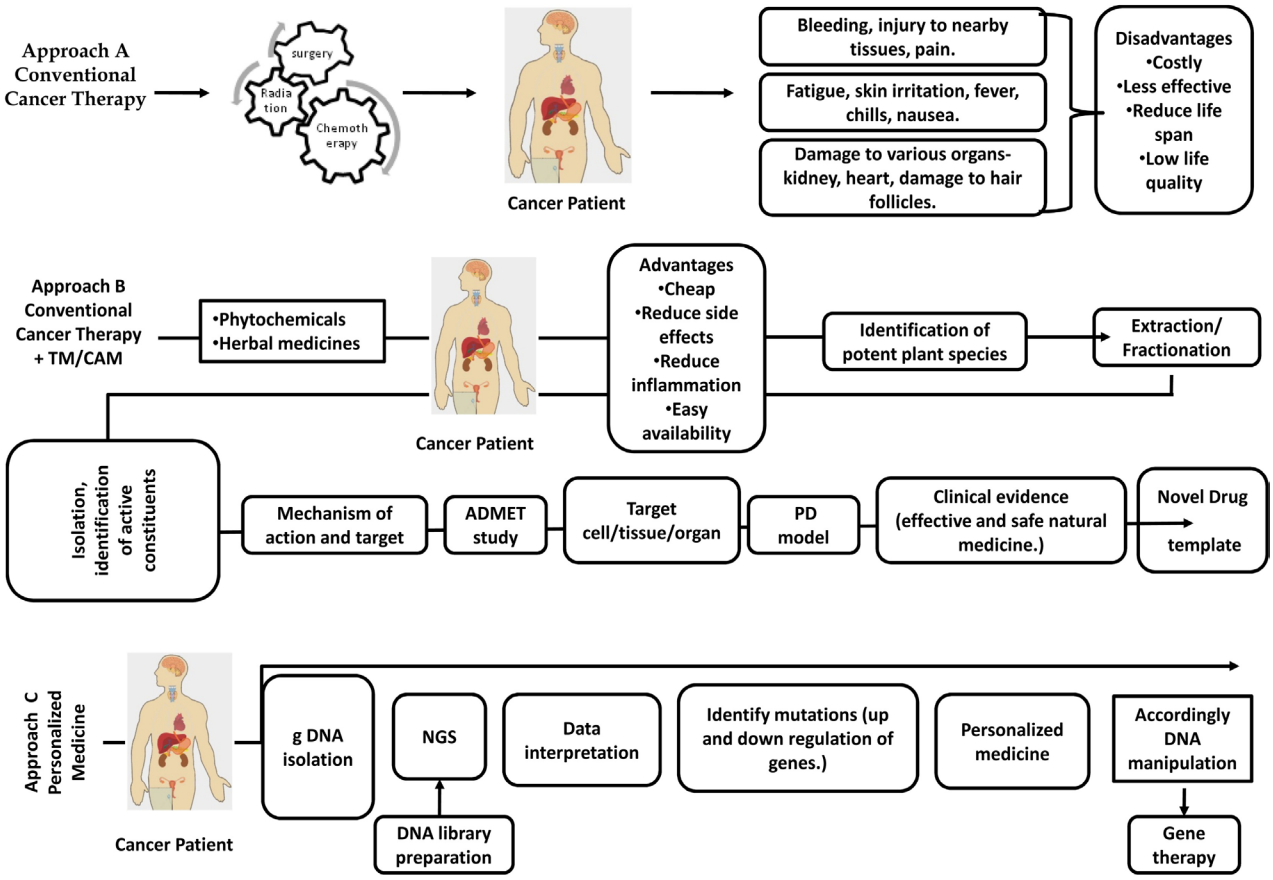

Figure 1. Approach A: Conventional approach used by clinicians commonly including surgery, chemotherapy and radiation therapy; Approach B: Combination therapy including Conventional Cancer therapy and Traditional medicine/complementary alternative medicine (active secondary metabolite with chemo-drugs); Approach C: Future prospects toward the cancer therapy included personalized medicine. *ADMET = Absorption, Distribution, Metabolism, Excretion, Toxicity. *PK/PD = Pharmacokinetics/Pharmacodynamics. *g DNA= genomic DNA. *NGS= Next genome sequencing.

focuses on identifying and isolating active ingredients rather than studying the medicinal properties of the whole plant [172]. Despite the remarkable progress in the organic synthetic chemistry, over 25% of prescribed medicines are derived directly or indirectly from plants which need to be further explored for better clinical intervention in therapeutics [166].

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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