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Review Article

ANTICANCER HERBAL DRUGS AND THEIR IMPROVEMENT THROUGH NOVEL DRUG DELIVERY APPROACHES

Manish Mathur* and S. Sundaramoorthy

*Plant Ecology Laboratory, Department of Botany, Jai Narain Vyas University, Jodhpur, Rajasthan 342 008 (India); **email: *ravi_mm2099@yahoo.com*

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ABSTRACT

Cancer is one of the most devastating diseases that involves various cellular and genetic alternations and globally is 2nd leading cause of death in humans. Alternative medicines and their by-products provide a positive hope to manage cancer. However, non-specific bio-distribution and targeting, less water solubility, poor oral bio-availability and low therapeutic efficacy limit the pharmacological properties of conventional anti-cancer herbal drugs. In this review an attempt has been made to discuss about the mechanism and therapeutic efficacy of twenty different anti-cancerous herbal drugs with focus on their best utility. Different techniques of novel drug delivery systems (NDDS) like nano-particles, phyto-complex, liposome, ethosome, nano-emulsion and microsphere have been discussed as potential tools to remove various constraints associated with these herbal drugs. Various important issues related with novel drug carriers like their generalized mode of action, their potential advantages over conventional drugs, future opportunities, technological challenges and possible steps to patch up the existing gaps have been discussed.

Key words: Cancer, herbal drugs, novel drug delivery approaches

1. INTRODUCTION

According to the International Agency for Research on Cancer (IARC) the cancer is a leading cause of death worldwide which inflicted 7.6 million deaths (~13% of all deaths) only in 2008 (Nirmala *et al.,* 2011). Colorectal, lung, female breast and prostate cancers are main contributors to such deaths in most parts of the world causing a loss of 18-50% total healthy years (Soeriomataram *et al.,* 2012). About 47% cancer cases and 55% cancer deaths occur in less developed countries, the countries having low or medium level of human development index (HDI). The trends in major cancers indicate that cancer harms will increase to 22 million new cases each year by 2030, indicating 73% hike over year 2008 [81% in low and middle HDI countries and 69% in high and very high HDI countries]. In India 7,137 deaths out of 1,22,429 cases were due to cancer in 2010 and estimated 71% cancer death occurred in the age range of 30 to 69 years, so showing age-specific trend in cancer diseases (Dikshit *et al.,* 2012).

Conventional drugs suffer because of their low aqueous solubility and physical stability, reduced absorption, rapid metabolism and instability under high acidic conditions. To combat these constraints intense research is focused on various sources to develop novel anti-cancer drugs. Plants have proved valuable natural anti-cancer therapy source. Increasing number of cancer patients currently use complementary and alternative medicines in conjunction with conventional chemotherapeutic treatments (Pathak and Katiyar, 2007). Balachandran and Govindrajan (2005) have reported pharmacological actions of 40 anti-cancer herbal drugs while Bhanot *et al.* (2011) listed 117 plants having anti-cancer properties.

Plant secondary metabolites have proved an excellent reservoir of new anti-cancer compounds and there are four major structural classes of anti-cancerous alkaloid compounds derived from plants *Vinca alkaloids, Epipodophyllotoxin lignans, Taxane diterpenoids* and *Camptothecin quinoline.* How-

*Address for correspondence: Manish Mathur, 18E/564 Chopasni Housing Board, Jodhpur, Rajasthan

ever, for safe and optimal use of anticancer herbal medicines, their pharmacokinetic must be evaluated in humans and most of such studies are focused mainly on a small number of herbal medicines including curcumin, ginseng, ginkgo, ginger and milk thistle (Chen *et al.,* 2011). Despite wide adaptability of herbal drugs, pharmacokinetic and delivery of herbal drugs require modification so as to achieve sustained drug release and increase patient compliance. The efficacy of many herbal drugs is often limited by their unspecific site of action. In most cases (conventional dosage forms) only a meager amount of administered dose reaches the target site and bulk of administered drug gets distributed throughout the body in accordance with its physicochemical and biochemical properties such as low solubility, reduced absorption, rapid metabolism, etc. Novel drug delivery systems (NDDS) are currently under development so as to lessen drug degradation, reduce dosage and its toxicity, increase solubility and stability, and improve tissue macrophages (Kumar and Rai, 2012a). NDDS are advantageous in delivering the herbal drug at predetermined rate and exhibit site-specific action. The present review is aimed to provide an overview of various anti-cancer herbal drugs and their improvement through novel drug delivery approaches, incorporating herbal active ingredient, their mode of action, factors affecting their efficiency, preparation methods of novel formulation and the potential advantages.

2. A GENERALIZED MODE OF ACTION OF NDDS

In cancer treatment six major types of drug delivery system are currently in use including both orthodox medicine and natural drugs. These are i) direct introduction of anticancer drug into tumor, ii) systemic delivery targeted to tumor, iii) drug delivery targeted to blood vessels of tumor, iv) special formulation and carriers of anticancer drugs, v) trans-membrane drug delivery to intracellular targets and vi) biological therapies. An ideal carrier for target drug delivery system should, therefore, have three pre-requisites for their functions: a) specific target effects, b) sufficiently strong adsorptive effects for anticancer drugs to ensure that drugs are transported to the effect-relevant sites; and c) release the drugs in effect-relevant sites. General advantages of NDDS over conventional drug delivery are summarized in Fig. 1.

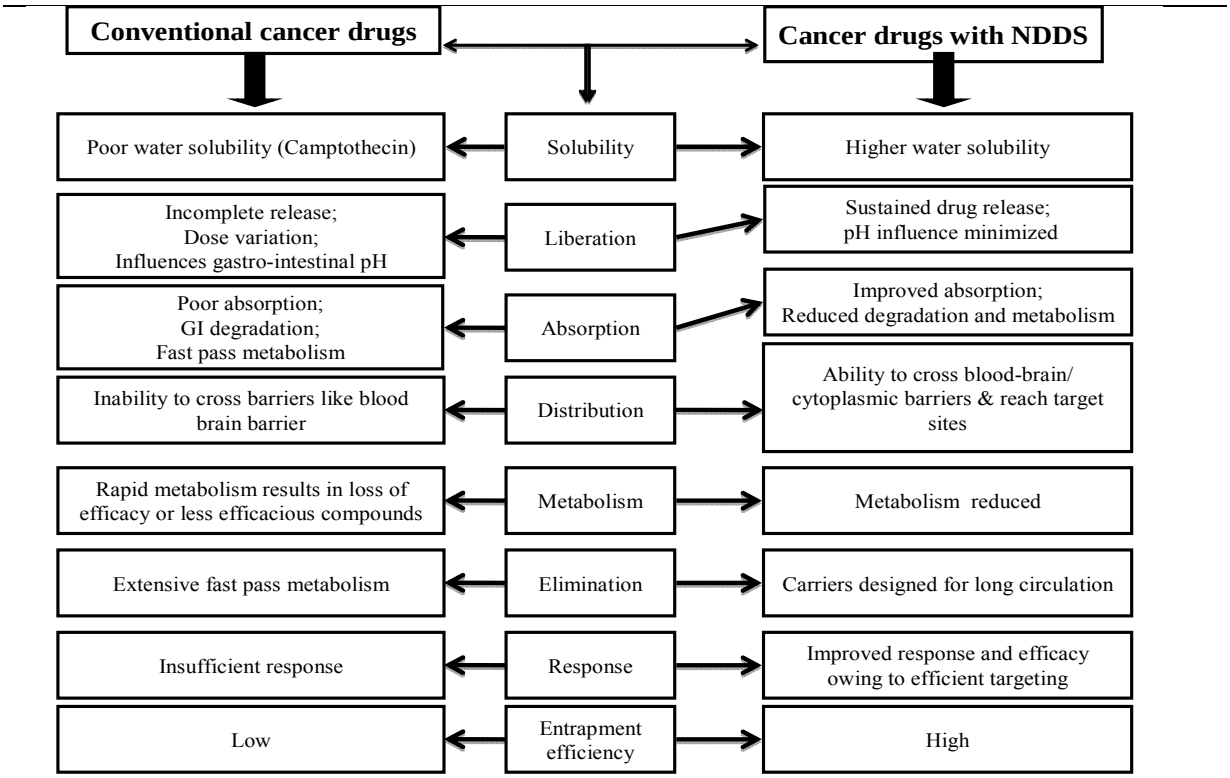

Fig. 1: Difference between conventional and NDDS techniques related with cancer therapy

NDDS are known to act by different mechanisms; however the two most accepted explanations behind the success of passively targeted-NDDS developed for cancer treatment are: a) enhanced permeability and retention (EPR) effect and b) possession of altered pharmaco-kinetic (PK) characteristics that are distinct from the encapsulated drug. The EPR effect is a property by which certain sizes of molecules (like nano-particles, liposome or phyto-complex drugs) tend to accumulate in Tumor tissue much more than they do in normal tissues (Patankar and Waterouse, 2012). EPR-based targeting relies on exploiting the leaky vasculature present at the tumor site (Fig. 2). The examples of EPR based NNDS systems are nano-particles of paciltaxel and *Artemissia annua*, liposome of camptothecin, silymarins, ampelopsin, transferosome of curcumin, ethosome of triptolide, phyto-complex of *Vaccinium myrillus,* etc.

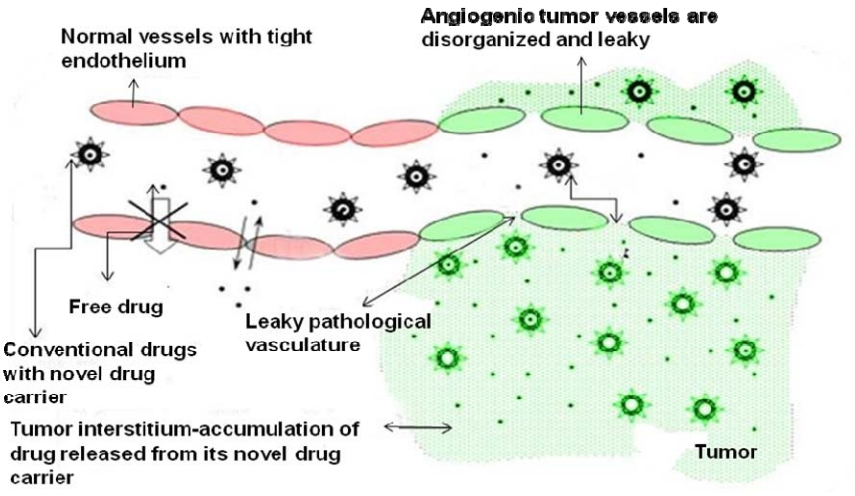

Fig. 2: Enhanced permeability and retention (EPR) effect

3. TYES OF DRUG DELIVERY SYSTEMS

In phyto-formulation research, developing nano-dosage forms like polymeric nano-particles, nano-capsules, liposome, phyto-complex, nanoemulsion, ethosomes, pronisomes, floating drug delivery system, micro-emulsions, etc. are advantageous as these enhance the solubility, bioavailability and stability of drug, provide protection from toxicity, enhance pharmacological activity and protect the drug from physical and chemical degradation (Saraf, 2010; Thakur *et al.,* 2011; Kumar and Rai, 2012a). The various types of novel drug delivery approaches used are summarized in Table 1 along with their

Table 1: Various novel drug delivery systems (NDDS) and their advantages

NDDS types	Description	Advantages
Nano-particles	Nano-particulate drug carriers, including a class of particles with a diameter of 10–1000 nm, are drug-loaded particles prepared by taking natural polymer or synthetic chemicals as the carrier.	a) Nano-carriers have more surface area and potential to increase solubility, enhance bioavailability, improve controlled release and enable precision targeting of entrapped compounds than micrometer size carriers; b) Amount of material required to exert specific effect when encapsulated to nano-carriers is less than un-encapsulated one owing to the improved stability and targeting; c) Delivery system nanonization is efficient for both hydrophilic and hydrophobic herbal drugs and can be formulated for lymphatic, brain, arterial walls, lung, liver and spleen system (Pathak and Katiyar, 2007).
Phytocomplex	It is a patented technology that incorporates standardized plant extracts or water soluble phyto-constituents (flavanoids and terpenoids) into phospholipids to produce lipid compatible molecular complex.	a) Enhances absorption of lipid insoluble phyto-constituents and reduces dose requirement by improving the absorption of active constituents. b) Besides serving as a carrier phosphatidylcholine it acts as hepatoprotective so improves various liver disorders. c) Chemicals bonds are formed between phosphatidyl-choline molecule and phyto-constituent so phytocomplex shows better stability.

Liposomes	Liposomes are lipid vesicles mainly composed of one or multiple lipid bi-layers composed of mixtures of phosphatidyl-cholines with long or short hydrocarbon chains.	The technique is efficiently utilized for enhancing the therapeutic index of anti-cancer agents, either by increasing the drug concentration in tumor cells and or by decreasing the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon and by utilizing targeting strategies (Sharma *et al.,* 2006).
Emulsions	Emulsion is a biphasic system in which one phase in intimately dispersed in other phase in the form of minute droplets. In emulsion, one phase is always water or aqueous phase, and the other phase is oily liquid, i.e. non-aqueous	a) Emulsion drug delivery system is targeted or well distributed due to affinity for lymph. b) Emulsion releases drug for a long time as it is packed in the inner phase and makes direct contact with body and tissues. c) Apart from targeted sustained release, the herbal drug in emulsion formulation strengthens stability of hydrolyzed materials, improves the penetrability of drugs to the skin and mucous, and reduces drug stimulus (Saraf, 2010)
Transfersomes	Transfersomes are made up of phospholipids supplemented with single chain surfactant with high radius of curvature which acts as edge activators to provide vesicle elasticity and deformability (Cevc *et al.,* 1996).	a) Possess unique ability to get accommodated with a wide range of solubility; b) Act as an efficient carrier for both low and high molecular weight drugs, e.g. analgesic, corticosteroids, hormones, anticancer drugs, insulin, proteins, etc. with high entrapment efficiency and a unique advantage of protection of the encapsulated drug, from metabolic degradation (Prajapati *et al.,* 2011).
Ethosomes	Ethosome are soft, malleable lipid vesicles composed mainly of phospholipids, alcohol (ethanol or isopropyl) in relatively high concentration (20-45%) and water (Rakesh and Anoop, 2012).	a) As a novel liposome, ethosomes are specially suitable as topical or trans-dermal administration carrier; b) Have high deformability and entrapment efficiency and can penetrate through the skin; c) The physical and chemical properties of ethosomes make the delivery of drug through stratum corneum into a deeper skin layer efficiently or even into the blood circulation (Dayan and Touitou*.,* 2000)
Microspheres	Microspheres are characteristically free flowing powders consisting of synthetic biodegradable polymers/ proteins and ideally have particle size <200 μm (Singh *et al.,* 2011).	a) Can be ingested or injected and tailored for desired release profiles; b) Used as site-specific delivery of drug and in some cases even provide organ-targeted release (Saraf, 2010).
Lipoprotein	Lipoproteins are endogenous particles that transport lipids through blood to various cell types where they are recognized and taken up via specific receptors.	a) Considered excellent candidates for targeted delivery of drugs to various tissues; b) Lipid encapsulation substantially extends residence time in circulation of natural drug like paclitaxel (Lacko *et al.* 2005)
Dendrimer	Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches.	a) An alternative attractive strategy to redesign drugs so as to combat unfavorable properties of small molecules (like insolubility) by larger characteristics of macromolecule; b) Flexible branches of dendrimers provide tailored sanctuary containing voids which provide a refuge from the outside environment. c) Paclitaxel and docetaxel (Ooya *et al*., 2004) as well as the anticancer agent 10-hydroxycamptothecin (Morgan *et al*., 2003), have been successfully encapsulated.
Microemulsion	Microemulsions are macro-scopically homogeneous, optically fully transparent fluids having more than one liquid phase.	a) Have small diameter, good stability and easy to prepare and increase the solubility of drugs, b) Provide a novel delivery of administration for low water-soluble drugs. c) Improves the absorption of herbal drugs

specific potential advantages. In novel drug delivery technology, the control of drug distribution is achieved by incorporating the drug in carrier system or by changing the drug structure at molecular level (Atmakuri and Dathi, 2010). Thus NDDS have potential to address various problems related to herbal medicine practice (HMP).

4. PHYTO-FORMULATIONS AND THEIR DELIVERY SYSTEMS

Paclitaxel

Paclitaxel (PTX, 5β,20-epoxy-l,2 α, 4, 7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester; Fig. 3), a major anticancer drug isolated from the bark of *Taxus brevifolia* (Nutt.) [Taxaceae], has anti-neoplastic activity particularly against various types of solid tumors. PTX is approved in many countries for use as second line treatment for ovarian and breast cancers (Singla *et al.,* 2002). PTX disrupts dynamic equilibrium within the microtubule system and blocks cells in late G_2 and M phases of cell cycle thereby inhibit cell replication. However, high lattice energy of paclitaxel results in very limited aqueous solubility {approx. 0.7-30 μg ml^{-1}} (Singla *et al.,* 2002) contributing to only 2 commercialized forms of injectable paclitaxel [Taxol® and Abraxane®]. Taxol® is 50:50 (v/v) mixtures of Cremophor EL (polyethoxylated castor oil) and dehydrated alcohol. In clinical therapy, high doses of anti-histamines and gluococorticoids are co-administered to overcome such adverse effects, but this strategy has raised the possibility of additional pharmacokinetic and pharmaco-dynamic issues with paclitaxel. To eliminate Cremophor EL from paclitaxel formulation, many alternative Cremophor EL-free formulations of paclitaxel have been investigated. Abraxane® is one of those Cremophor EL-free paclitaxel formulations approved by FDA in 2005. Despite its improved clinical profile, Abraxane® has not replaced Taxol in cancer chemotherapy mostly due to its high cost. Therefore, alternative cost-effective parental formulations of paclitaxel are still needed (Dong *et al.,* 2009).

Nano-particulate drug carriers include a class of particles with a diameter range of 10 to 1000 nm. Nano-carriers provide more surface area and have potential to increase solubility, enhance bioavailability, improve controlled release, and enable precision targeting of entrapped compounds to a greater extent as compared to micrometer size carriers. Incorporation of PTX into nano-particles enhanced its anti-tumor activity as compared to Taxol® (Breuning *et al.,* 2008). In mice PTX-loaded nano-particles have shown noticeable anti-tumor efficacy and enhanced survival rates than Taxol®. Moreover, nano-particles escape from vasculature through leaky endothelial tissues that surround the tumor and accumulate in certain solid tumors by enhanced permeation and retention (EPR) effect. Nano-particles are also prepared by interfacial deposition method {nano-precipitation}, sequential simplex optimization method and through emulsion solvent evaporation method (Dong *et al.,* 2009). Pacilitaxel nano-particles are stable at 4°C over 3 months thus enhance drug stability, support sustained drug release and improve bioavailability.

Docetaxel (Taxotere®), a semi-synthetic derivative of paclitaxel, has been found more effective and can be used in patients who are resistant to paclitaxel. The active agents of this anti-mitotic drug bind to the polymerized microtubules and prevent normal mitosis. Emulsions of *Taxus brevifolia* (Docetaxel) have been prepared by homogenization method that improves the bioavailability, improves solubilization ability of hydrophilic drug and increases residence time (Yine *et al*., 2009).

Curcumin

Curcumin or diferuloylmethane is a yellow polyphenol extracted from the rhizome of turmeric (*Curcuma longa* L.) [Zingiberaceae]. The anti-cancer properties of this drug have been demonstrated in all the steps of cancer development viz., initiation, promotion and progression of cancer (Sarkar and Deshmukh, 2011). Despite being efficacious and safe for cancer therapy and chemo-prevention; curcumin has by no means been embraced by the cancer community as a "panacea for all ills". The vital reason for this reticence is the reduced bioavailability of orally administered curcumin, and the therapeutic effects are essentially restricted to tubular lower GI tract {i.e. colorectum} (Sharma *et al.,* 2004). Nano-particle-based drug delivery approaches have potential for rendering hydrophobic properties of curcumin thus circumvent the pitfalls of poor solubility. Nano-particles of curcumin

(nano-curcumin) have been prepared by wet-milling and micro-emulsion techniques (Bisht *et al.,* 2007). Unlike curcumin, nano-curcumin is water dispersible in absence of any surfactants. NanoCurc^{TM}, a recently described polymeric nano-particle formulation of curcumin, has been used to inhibit malignant brain tumor growth through modulation of cell proliferation, survival and stem cell phenotype (Lim *et al.,* 2011). Curcumin phyto-complex has been prepared through curcumin-phospholipids complexation that increases its antioxidant anticancer properties and bioavailability (Maiti *et al.,* 2007). Dhule *et al.* (2012) prepared liposome-based curcumin formulation through ethanol injection method and the novel drug possessed high circulation and entrapment efficiency as compared to its traditional dose. On the other hand Patel *et al.* (2009) prepared curcumin transfersomes through hand shaking method using surfactant. This transfersome curcumin has high permeation capability. The emulsion formulation for this drug has been prepared through drawing ternary phase method (Zhao *et al.,* 2010) that improved its aqueous solubility, stability and oral bioavailability. Kumar and Rai (2012b) have prepared curcumin floating microspheres through quasi-emulsion-solvent method that supports sustained drug release of this drug.

Quercetin

Quercetin, 3, 3′,4′,5′-7-pentahydroxy flavonoid (Fig. 3) excreted from air-dried plant part of *Spohora japonica* L. [Leguminosae] mainly from the bark and leaves. The antioxidant activity of qercetin is higher than well-known antioxidant molecules such as ascorbyl, trolox, etc. The antioxidant properties are attributed to the number and position of free hydroxyl groups in quercetin molecule. The flavonoid

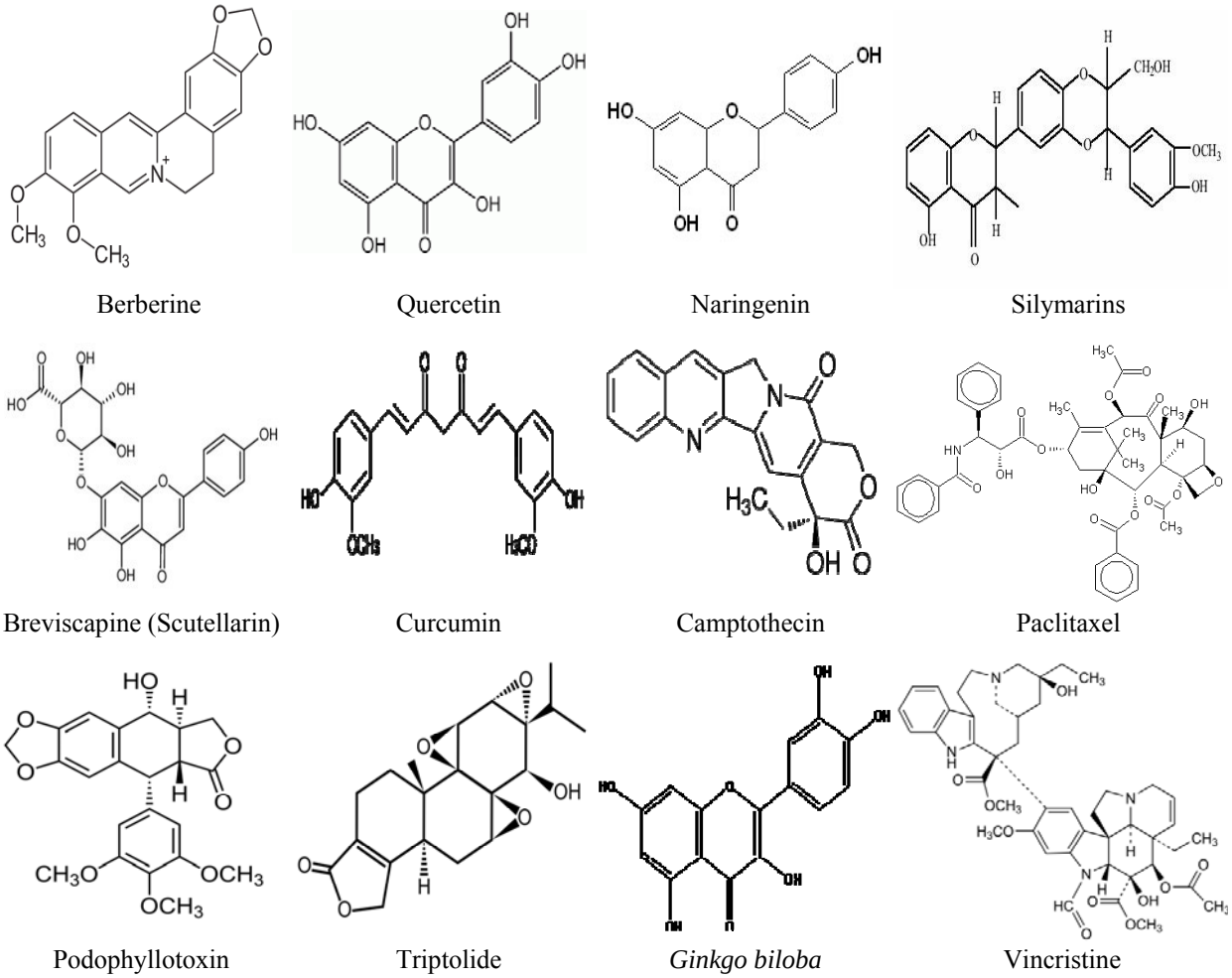

Fig. 3: Chemical structures of some anticancer herbal drugs

glycosides are rapidly hydrolyzed in colon by bacterial activity to generate quercetin aglycones which are further converted to quercetin-3-glucuronide (Q3GA), a major anti-oxidative quercetin metabolite in human plasma. This molecule is retained in large intestine for about 6 h after oral administration. However, it is chemically unstable, especially in aqueous alkaline medium, which possibly involves the loss of hydroxyl ions on C-ring of quercetin. Apart from the antioxidant activity, this molecule shows anticancer and antiviral activities (Schaab *et al.,* 2006). In spite of these wide spectrum pharmacological properties, the use of quercetin in pharmaceutical field is limited due to its low aqueous solubility, instability in physiological medium, poor bioavailability, less permeability, instability and extensive fast pass metabolism before reaching the systemic circulation (Ratnam *et al.,* 2006). To improve aqueous solubility and stability Zhang *et al.* (2008) have prepared quercetin-loaded nano-particles with gelation of chitosan with tripolyphosphate anions. Kumar *et al.* (2010) developed poly (D, L-lactide) (PLA) nano-particles by solvent evaporation method while Fang *et al.* (2011) prepared quercetin nano-particles by using bovine serum albumin.

The nano-encapsulation of quercetin into PLA nano-particles significantly improved therapeutic efficacy and bioavailability. Kumar *et al.* (2010) reported that 40-45% quercetin was released *in vitro* within 0.5 h showing rapid burst release. Phyto-complex formulation enhances therapeutic efficacy and oral absorption of natural drug. On the other hand Priperm *et al.* (2008) prepared its liposomal formulation by using mixture of egg, phosphotidylcholine and quercetin. The formulation reduced the dose requirement and enhanced penetration in blood brain barrier and bioavailability.

Breviscapine

Breviscapine (BVP) is a well-known bioactive flavonoid ingredient (4',5,6-tri-hydroxyflavone-7-glucuronide) extracted from whole plant of perennial herb *Erigeron breviscapus* Vant. [Asteraceae] and has therapeutic effect on lung and vascular diseases. Breviscapine is useful in inhibiting pulmonary fibrosis and reduces the damage due to oxygen-derived free radicals in bleomycin (Xiong *et al.,* 2011). Scutellarin [4′,5,6-tetra-hydroxyflavone-7-*O*-glucuronide] (Fig. 3), the major active component of breviscapine, prevents vascular endothelial dysfunction in diabetic rats, and is capable of inhibiting the proliferation of high glucose and hypoxia-stimulated proliferation of human retinal endothelial cells [HREC] (Gao *et al.,* 2008). Scutellarin also inhibits platelet aggregation induced by arachidonic acid, adenosine diphosphate and platelet activating factor.

It is well-known that cerebrovascular, cardiovascular and cancerous diseases always need a drug possessing more bioavailability and long half-life. However, BVP has very short half-life and poor bio-availability for oral administration. Scutellarin has poor water solubility but is soluble in ether, chloroform, ethanol, acetic acid and acetone. It is stable only under acidic conditions and unstable in alkaline solutions. The lipid emulsions (LE, oil-in-water emulsions stabilized by lipid surfactants), used as carrier for breviscapine, might improve the chemical stability of drug, increase drug loading efficiency, decrease irritation on the surrounding tissue as well as control and modify its pharmacokinetics and tissue distribution. Xiong *et al.* (2011) have reported that nano-coating increases plasma concentration and pharmacological activity of breviscapine and enhances blood circulation.

Naringenin

Naringenin [4′,5,7-trihydroxyflavanone, NAR] (Fig 3), a natural flavonoid aglycone of naringin, is widely distributed in citrus fruits (Dembinski *et al.,* 2004), tomatoes (Gall *et al.,* 2003), grapefruit (Erlund *et al.,* 2001) and cocoa (Stark *et al.,* 2005). It is a well-known antioxidant compound and this property is attributed to its structure-activity relationship. The number of hydroxyl substitutions of NAR can donate hydrogen to reactive oxygen species thereby allow acquisition of stable structure and scavenge these free radicals. NAR has extensively been investigated for its pharmacological activities including anti-tumor, hepato-protective and anti-inflammatory effects (Kanno *et al.,* 2005). *In vitro* anti-carcinogenesis assays have revealed that naringenin inhibits aflatoxin B_1-induced carcinogenesis. Despite free radical scavenging ability and pharmacological activities, the clinical studies exploring

various schedules of NAR administration have been hampered by its extreme water insolubility. The absolute bioavailability of NAR was 4% in rabbits when administered orally (Hsiu *et al.,* 2002).

Yen *et al.* (2008) have developed a novel naringenin-loaded nano-particles (NARN) delivery system using Eudragit® E and polyvinyl alcohol as carriers by a simple nano-precipitation technique. Nano-particles delivery system considerably improved the physicochemical profile of naringenin and resulted in enhanced drug release. Further, NARN showed better anti-tumor effect than NAR on oral administration through enhanced antioxidant and anti-apoptotic activities in rat model. The nano-precipitation technique possesses numerous advantages, being relatively straightforward, rapid and offer reproducible particle size with a narrow distribution (Chen *et al.,* 2005). NARN has successfully changed several original physicochemical properties of naringenin like reduction in particle size, rendering crystalline structure amorphous and improvement in drug release rate. Naringenin, a phosphospholipid complex (Phyto-complex), not only enhanced its bioavailability but also improved its duration of action (Semalty, 2010).

Silymarins

Silymarins, a group of naturally occuring penta-cyclic triterpenoid compound extracted from the fruit of milk thistle *Silybum marianum* L. [Asteraceae], exhibit remarkable therapeutic effect in many liver disorders. Silibinin is the main biological active component largely responsible for its antihepatotoxic activity (El-Samaligy *et al.,* 2006). Various clinical and pharmacological effects of silymarin have been reported such as targeting cancer cell metastasis (Rajamanickam *et al.,* 2010) and inducing activation of death receptor and mitochondrial apoptotic pathways in human breast cancer MCF7 cells (Woo *et al.,* 2007). Davis-Searles *et al.* (2005) have identified seven distinct lignan and flavonoid compounds from commercial silymarin extracts. Among these, four compounds namely silybin A, silybin B, isosilybin A and isosilybin B showed most consistent anti-proliferative effect in three different human prostate carcinoma LNCaP, DU145 and PC3 cell lines. Ramasamy and Agarwal (2008) have shown that isosilybin A and B exert growth inhibition and cell death together with a strong G_1 arrest and apoptosis in human prostate carcinoma LNCaP and 22Rv1 cell. However, the poor solubility of silymarins in water and oil has resulted in permeation through intestinal epithelial membrane and low absorption in gastrointestinal tracts of rats (Wu *et al.,* 2006). Kumar (2010) have prepared silymarin-loaded solid lipid nano-particles (SlySLNs) by cold homogenization technique and characterized them for mean diameter, entrapment efficiency and drug loading. Under optimal conditions, the prepared SlySLNs have a mean diameter of 190.9 nm, entrapment efficiency of 95.9%, and drug loading of 8.6% (Raffa *et al.,* 2010).

He *et al.* (2005) found that the area under plasma concentration (AUC) of 150 nm SLNs (prepared by Compritol 888 as the material and silymarin as a model drug) was 2.08-fold higher than that of 500 nm SLNs and 2.54-fold higher than that of 1000 nm SLNs administered orally to rats ($p<0.05$). Thus oral bioavailability of 150 nm SLNs was remarkably higher than other sizes. Oral bioavailability of SlySLNs in beagle dogs confirmed that SLN is a good carrier and improves oral bioavailability of poorly soluble drugs (He *et al.,* 2005). Kid and Head (2005) have reported that the absorption capacity of siliybin phyto-complex was 7 times higher from its conventional dose. Mohamed *et al.* (2006) using liposomal formulation of this drug observed that the interaction between silymarin and phospholipids led to increase in permeation thereby enhanced its bioavailability. Emulsion formulation of this drug has been prepared through emulsification method (Song *et al.,* 2005) that supports sustained release of formulation.

Triptolide

Triptolide, a diterpenoid triepoxides isolated from extract of whole plant of *Tripterygium wilfordii* Hook. [Celastraceae], has antitumor activities by suppressing the growth and inducing apoptosis of broad range of human tumor cells. Triptolide reduces the expression of cell cycle regulators and survival genes (Kiviharju *et al.,* 2002); however, its clinical uses are restricted due to its scarce water solubility and some toxic effects. Guan *et al.* (2011) have prepared nano-particle and emulsion formulations of triptolide by emulsification ultrasound and high pressured homogenization methods, respectively, that enhanced the penetration of drug through stratum corneum by increase hydration. To increase its stability and reduce

side effects, Li *et al.* (2007) prepared liposome triptolide through thin film depression method. Chen *et al.*(2012a) prepared its ethosome formulation through combined filming-rehydration and ultrasonic methods, this formulation exhibits high entrapment efficiency and shows good precutaneous permeability.

Camptothecin

Camptothecin (CPT) is a cytotoxic quinoline alkaloid isolated from bark and stem of 'Happy tree' (*Camptotehca acuminata* Decne.) [Nyssaceae]. It has anticancer properties and inhibits DNA enzyme topoisomerase. CPT shows poor aqueous solubility and severe toxicity. To overcome these limitations certain analogues of CPT like topotecan, irinotecan (CPT-11), 9-amino-camptothecin (9-AC), lurtotecan and rubitecan have been synthesized. These analogs inhibit DNA topoisomerase I which plays a major role in various DNA functions like replication and transcription. The camptothecin molecule has a S-configured lactone form and a carboxylate form which is responsible for anti-cancer activity. Topotecan is found clinically effective in patients with epithelial ovarian cancer and small cell lung cancer as a second-line treatment. Irinotecan acts as 1st and 2nd line treatment for metastatic colorectal cancer. These synthetic analog seems to have better aqueous solubility, tumor efficiency and lesser toxic effects as compared to camptothecin (Nirmala *et al.,* 2011). However, these analogues are required larger in quantity to achieve high efficacy and also exhibit slow pharmacological actions (Kunii *et al.,* 2007).

CPT loaded nano-particles by using poly-(DL-lactic acid) (PLA) and poly-(ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol) (PEG-PPG-PEG) have been prepared by Kunii *et al.* (2007); while Chen *et al.* (2012b) prepared CPT nano-particles by using self-assembly method. Compared to the traditional drugs and their derivatives, nano-loaded CPT have high water solubility and high dose retention in body and are effective at lower concentrations.

Berberine

Berberine, a naturally occurring iso-quinoline alkaloid, is present in the roots, rhizome and stem bark of a number of medicinal plants such as *Berberis vulgaris*, L. [Berberidaceae], *Hydrastis Canadensis,* L. [Ranunculaceae], *Phwllodendron amurense* Rupr. [Rutaceae], *Coptis chinensis* Finet & Gagnepain [Ranunculaceae] and *Tinospora cordifolia* Thunb. [Menispermaceae]. Berberine has tremendous potential to cure many physiological disorders. Berberine inhibits activator protein 1, a key transcription factor in inflammation and carcinogenesis, in human cell lines (Fukuda *et al.,* 1999a), possesses anti-tumor properties and effectively inhibits cyclooxygenase-2 transcriptional activity in human colon cancer cells (Fukuda *et al.,* 1999b). Significant killing effects of berberine on human malignant brain tumor, esophageal cancer, leukemia and human colon cancer cell lines have been achieved (Roy *et al.,* 2005). The traditional drug has shown poor pharmacokinetic properties and less bioavailability and absorption. Wu and Ging (2007) have prepared its nano-particle and emulsion containing formulation through ionic gelation and drawing ternary phase techniques, respectively. These formulations support sustained drug release, residence time and absorption.

Ginkgo biloba

Ginkgo biloba L. [Ginkgoaceae] leaf extract has widely been marketed for its brain cell activation properties (Tadano and Kisara, 1997). However, the existing powder of *G. biloba* extract as such has not shown any remarkable effect for brain cell activation due to bigger its granule size and insufficient absorption of active ingredient into the body system because plant cell wall is not destroyed. Further, *G. biloba* contains ginkgolic acid which is a kind of hydrophobic salicylic acid derivative causing allergy or polyphenolic compound (proanthocyanidin) with water solubility and browning reaction. These need to be removed when *G. biloba* extract is used in drug, food or cosmetic materials. Various molecular, cellular and whole animal models have revealed that leaf extracts of *G. biloba* have anticancer (chemo-preventive) properties owing to their antioxidant, anti-angiogenic and gene-regulatory actions. In human, *Ginkgo* extracts inhibit the formation of radiation-induced (chromosome-damaging) clastogenic factors and ultra-violet light-induced oxidative stress-effects that may also be associated with anticancer activity (Vandana and Suresh, 2008). Flavonoid and terpenoid constituents of *Ginkgo* extracts may act in a complementary manner to inhibit several carcinogenesis-related processes; therefore the whole extracts may be required

for optimal effects (DeFeudis *et al.,* 2003). Mesallamy *et al.* (2011) have reported that *G. biloba* extract has beneficial protective effect against hepato-carcinogenesis induced by N-nitroso-diethylamine (NDEA). However, *G. biloba* extract possesses poor oral bioavailability and absorption. Shinji *et al.* (2011) have demonstrated that the extract of *G. biloba* containing nano-particles increases acetylcholine-releasing activity from cerebral cortical synapses and improves stimulative response of hippocampal pyramidal cell. Thus, the nano-sized *G. biloba* extract is expected to activate brain cell and work on the treatment of Alzheimer's dementia (like loss of memory, thinking, language, judgment and behaviou). Ginkgo Select® a phyto-complex base product of *G. bioloba* exhibits improved oral bioavailability and absorbability, induces hepato-protective effect and inhibits lipid peroxidation (Naik and Panda, 2008)

Catharantus roseus

A widely distributed evergreen tropical weed *Catharantus roseus* L. [Apocyanaceae] is used against inflammation, cancer, diabeteic and constipation and is also useful to overcome menstrual problem. The aerial parts of plant contain alkaloids ajmalicine, vindoline and catharanthine. Vindoline is enzymatically coupled with catharanthine to produce powerful cytotoxic dimeric alkaloid vinblastine (VBL), vincristine (VCR) and leurosidine. They inhibit cell proliferation by affecting the microtubular dynamics during mitosis and cause a characteristic block during mitosis leading to apoptosis. Vinorelbine (VRLB) and vindesine (VDS) are two semi-synthetic analogs obtained from active compounds which show potential activity against leukemia, lymphoma, advanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma when treated in combination with other chemotherapeutic drugs. Vinflunine, a bifluorinated derivative of vinorelbine exhibits superior anti-tumor activity as compared to other vinca alkaloids. They are all administered intravenously in their sulphate form. However, the solutions are fatal if administered through any other way and may cause tissue irritation if leaked out from the vein. Lu *et al.* (2007) have prepared transfersome of *C. rosesus* alkaloids by dry film ultrasonic dispersion method using lecithin and sodium deoxycholate in 70:20 ratio. These transfersomes penetrate skin and enter systemic circulation carrying VCR with good lymph targeting ability, which makes it probably a new lymphtic targeting drug delivery system.

Podophyllotoxin

Podophyllotoxin (POD) is obtained from the roots of *Podophyllum* species [Berberidaceae], namely *P. peltatum* L. and *P. emodi* Wallich. Epipodophyllotoxin is an isomer of podophyllotoxin. The two clinically important semi-synthetic analogs generated from epipodophyllo-toxin are etoposide and teniposide which have potential use in treating lymphomas, bronchial and testicular cancers (Shoeb, 2006). Podophyllin arrests multiplication of cancerous cells by breaking down the mircrotubules into smaller subunits thus inhibits cell division. The synthesis of podophyllotoxin is a multi-step process, involving many components and expensive reagents. The latest reported method for the synthesis of podophyllotoxin involves 5 steps and 20 reagents with 7.6% overall yield; further the synthesis problem is coupled with its slow pharmacological action thus limits the new derivatives research of podophyllotoxin core (Kumar and Alegria, 2010).

Chen *et al.* (2006) have evaluated solid lipid nano-particles (P-SLN) as topical carrier for epidermal targeting of podophyllotoxin by using high pressure homogenization method. They observed that P-SLN has good epidermal targeting effect and serves as a promising carrier for topical delivery of POD. Zhu *et al.* (2009) *in vitro* evaluated the anti-tumor properties of podophyllotoxin-loaded solid lipid nano-particles (prepared through solvent emulsification-evaporation method) and observed these to have sustained drug release, high anti-tumor efficiency and long term suppressive effect as compared to podophyllotoxin alone. Yan-Yan *et al.* (2010) prepared ethosomal formulation of podophyllotoxin by using freeze drying method which showed higher entrapment efficiency and therapeutic effect as compared to their traditional dose.

Artemisia annua

Artemisia annua L. [Asteraceae] is a single stemmed annual herb indigenous to Asia and grows to a height of about 2 m. Artemisinin or qinghaosu is the active principle of *Artemisia annua*. Artemisinins (ART)

have shown promising anti-cancer activities when tested *in vitro* and *in vivo* (Singh and Lai, 2001). Artemisinins contain an endoperoxide group, essential for their anti-malarial and anti-cancer activities. Like hydrogen peroxide (H_2O_2), artemisinin reacts with ferrous iron, Fe^{2+}, to generate radical species. The anticancer activity of artemisinin derivatives increases significantly when iron complexes are added in cell culture medium. A covalent conjugate of artemisinin and transferrin (ART-Tf), an iron transport protein in human, is actively taken up by cancer cells through transferrin receptor (TfR)-mediated endocytosis pathway and shows significantly higher anti-cancer activity than unconjugated artemisinin (Nakase *et al.,* 2009). Despite potent anti-malarial action, ART suffers from poor pharmaco-kinetic properties and short half-life. Artemisinin is chemically unstable and poorly soluble in water and oil (Padmanaban *et al.,* 2012). Chen *et al.* (2009) have developed nano-coated artemisinin through self assembly procedure by loading poly-electrolytes on natural drug crystals. These ART nanocapsules dispersed well in aqueous solutions with improved hydrophilicity. Chiara *et al.* (2005) have prepared its liposomal formulation by film method and sonication techniques which showed increased stability and better penetration into cytoplasmatic barrier.

Salvia miltiorrhiza

The dried roots of *Salvia miltiorrhiza* L. [Lamiaceae, Danshen] are widely used as medicines for promoting circulation and improving blood stasis. Danshen is extensively used for treatment of coronary heart, cerebrovascular diseases and hyperlipidemia (Zhou *et al.,* 2006). Salvianolic acid B is regarded as active components of *S. miltiorrhiza*. Tanshinone IIA is potential anticancer component extracted from the dried root of *S. miltiorrhiza* (Zhou *et al.,* 2005). Tanshinone IIA exerts cytotoxic effect on a number of human tumor cell lines. The induction of apoptosis is the key factor in contributing to the cytotoxic property of tanshinone IIA (Wang 2010). Neo-tanshinlactone, isolated from *S. miltiorrhiza* under *in vitro* conditions, showed significant inhibition against two human breast cancer cell lines, 10-fold more potent than tamoxifen citrate. Further, it potently inhibited an estrogen receptor over-expressing breast cancer cell so may serve as an anti-breast cancer medicine (Wang *et al.,* 2004). However, slow pharmacological action is a major drawback of this herbal drug. Liu *et al.* (2008) prepared nano-coated *S. miltiorrhiaza* that exhibited stronger antioxidant bioactivities and also the polar active constituent in nanotechnology samples were released faster than the traditionally powdered samples. Peng *et al.* (2008) enhanced oral bio-availability of salvianolic acid B by phospholipids complex loaded nano-particles.

Ampelopsin

Ampelopsin (3,5,7,3′,4′,5′-hexahydroxyl-2,3-dihydroflavonol), also known as ampeloptin or dihydro-myricetin, is purified component of tender stems, leaves or roots of herb *Ampelopsis cantoniensis* (Hook. and Arn.), Planch [Vitaceae]. Traditionally, used as detoxicant and for anti-inflammation functions, ampelopsin possesses powerful antineoplastic and antioxidant properties (Ye *et al.,* 2008). It induces apoptosis of cancer cells and inhibits the growth of tumor vessels by depressing the expression of VEGF and *b*FGF (Luo *et al.,* 2006). However, the drug suffers from poor physical stability and bioavailability (Ruan *et al.,* 2005). He *et al.* (2008) prepared liposomal formulation of this drug through film ultrasound method and were able to enhance its efficiency by modify its surface charge and membrane integrity.

Glycyrrhiza glabra

18 â-glycyrrhetic acid, a hydrolyzed derivative of glycyrrhezic acid, is an outstanding example of natural anticancer compound extracted from rhizome and root of *Glycyrrhiza glabra* L. [Fabaceae]. These components appear to possess anti-carcinogenic properties and inhibit abnormal cell proliferation and tumor formation and growth in breast, liver and skin cancers. Lower absorption and bio-availability are major drawbacks of this herbal drug. For improving its bioavailability Hou and Zhou (2008) prepared its nano-particles containing drug through rotary-evaporated film ultra-sonication method, while Gupta *et al.* (2007) prepared its phyto-complex formulation that increases its active gradient tolerability, absorption and its efficacy. Ethosomal formulation of this herbal drug has been prepared by Paolino *et*

al. (2005) through solvent dispersion method that increases its in-vitro percutanous permeation and significantly enhances its therapeutic efficiency.

Stephania tetrandra

Tetrandrine (TET) is a bis-benzylisoquinoline alkaloid isolated from the root of *Stephania tetrandra* Moore [Menispermaceae] and possesses broad spectrum pharmacological actions including plasma glucose lowering, anti-inflammatory, immunosuppressive and free radical scavenging activities (Li *et al.,* 1989). It exhibits cytotoxic effect on various types of cancer cells, including A549 (Lee *et al.,* 2002), Hep G2 (Yoo *et al.,* 2002), and T-HSC/Cl-6 (Zhao *et al.,* 2004) cells. Unspecific site of action and slow pharmacological properties are the major drawbacks associated with this drug. To enhance its efficacy and sustained drug release, Xiaoyan *et al.* (2008) developed its nanoparticles based drug through self-emulsification and solvent evaporating method.

Cladonia substellata

Among lichens *Cladonia substellata* Vain [Cladoniaceae] has highest concentration of usnic acid (98% of its chemical constitution) representing 7.3% of thallus dry weight (Huovinen and Ahti, 1986). Usnic acid exhibits anti-microbial activity against human and plant pathogens including virus and protozoa (Campanella *et al.,* 2002). Further, it possesses anti-proliferative, anti-inflammatory and analgesic activities and possesses cytotoxic and anti-tumor activities (Cocchietto *et al.,* 2002). Nevertheless, the practical use of usnic acid in therapy has rather been limited due to its poor solubility in water. To overcome this problem Ribeiro-Costa *et al.* (2004) through double emulsion method prepared PLGA-microspheres by micro-encapsulation of usnic acid and examined *in vitro* anti-tumour activity. They observed that usnic acid loaded-microspheres promoted 63% inhibition on tumor growth in comparison to 42% inhibition for free usnic acid. Lira *et al.* (2009) have prepared its liposomal formulation through hydration of thin lipid film method with sonication and reported an increase in the solubility and localization (targeted action) with prolonged release profile.

Scutellaria baicalensis

The dry roots of *Scutellaria baicalensis* Georgi [Lamiaceae] are widely used in traditional herbal medicine system as treatments for discomfort in chest, nausea, coughing, vomiting, acute dysentery, jaundice, carbuncles, sores, anti-xylotic, anti-cancer and threatened miscarriage (Gabrielska *et al.,* 1997). *In vitro* studies have revealed that *S. baicalensis* strongly inhibits the cell growth in all cancer cell lines; however, prostate and breast cancer cells are slightly more sensitive than other type of cancer cells (Ye *et al.,* 2002). Baicalin (5,6,7-trihydroxyflavone), the active ingredient of this drug, is practically insoluble in water but soluble in alcohol and has poor oral bioavailability and physical stability (Zhang *et al.,* 2011). To improve its stability and sustained release, Xue *et al.* (2007) have prepared its liposome based formulation through film dispersion method that supports its *in vitro* longitivity. To increase its oral bioavailability, Zhang *et al.* (2011) have prepared its nano-crystals based on anti-solvent re-crystallization followed by high pressure homogenization method, and reported 1.67 fold higher bioavailability as compared to its conventional drug.

Vaccinium myrtillus

Bilberry, *Vaccinium myrtillus* Rydb [Ericaceae], has very limited geographic distribution but has a well-established role in pharmacognosy. Biological properties of its fruit extract, rich in anthocyanins (malvidin 3-O-α-L-arabinopyranoside) include antioxidant capacity, astringent and antiseptic properties, ability to decrease the permeability and fragility of capillaries, inhibition of platelet aggregation and urinary tract infection and strengthening of collagen matrices via cross linkages (Laplaud *et al.,* 1997). Madhavi *et al.* (1998) have demonstrated that specific fractions isolated from fruits of *V. myrtillus* possessed potential anti-carcinogenic constituents. Fruit extracts were screened for their ability to induce the phase II xenobiotic detoxification enzyme quinone reductive (QR), an enzyme involved in detoxification of potential carcinogens and xenobiotics. A specific fraction isolated from the fruits was

an active QR inducer, indicative of the potential to inhibit the initiation stage of chemical carcinogenesis (Bomder *et al.,* 1996).

The higher concentration of phenolic compound suppressed its pharmacological properties by producing non-solubility in aqueous medium and poor absorption in gastro-intestinal tract (Martz *et al.,* 2010). To overcome these limitations, Indena (Italy) have developed phyto-complex technology based herbal commercial product Mitroselect®. It improves capillary tone and reduces abnormal blood vessel permeability and solubility of drug thus improves absorption of drug (Karparamban *et al.,* 2012).

Fungal and algal-derived anticancer molecules

There are currently two fungal-derived molecules that serve as templates for analogs used in clinical trials, Fumagillin and Illudin (Almedia, 2011). Fumagillin is produced by fungus *Aspergillus fumigatus*. It is an angiogenesis inhibitor, which suppresses the formation and growth of new blood vessels, by direct blocking endothelia cell proliferation. Semi-synthetic derivatives, such as TNP-470, PPI-2458 and CKD-732 have been tested for treatment of breast, prostate and brain cancer. Illudin isolated from basidiomycetes *Omphalotus illudens* has shown extreme cytotoxic activity against human leukemia cell line HL-60. Its semi-synthetic compound Irofulven has superior therapeutic index as compared to its natural sources. Li and Tao (2009) have tested the impact of *Fusarioun mairei* broth culture for the production of paclitaxel and found that co-culture system of plant and fungus yield paclitaxel 2-fold higher than cell suspension culture of *Taxus alone*.

Dhorajiya *et al.* (2012) have listed 25 different anti-cancer agents from marine world that includes alga like *Nostoc linckia, N. spongiaeforme, Acanthophora spicifera, Palmaria palmate, Sargassum thenbergii* and *Ascophyllum nodosum*, marine costal plants like *Ceriops decandra, Acanthus illicifolius, Calophyllum inophyllum* and *Exoecaria agallocha*. These marine sources possess anti-proliferative, anti-tumour, anti-cancer, anti-metastatics and fibrinolytic activities. On the other hand Mahdi and Fariba (2012) have pointed out the potentiality of cyanobacteria, sponges, molluscs and various soft corals for cancer treatment. Feng and Chien (2003), Fries (2003) and Mahdi and Fariba (2012) have reported the roles of various nanoparticles, dendromers, liposomes for enhancing the drug efficacy as well as their delivery system of above mentioned sources.

5. FUTURE OPPORTUNITIES AND CHALLENGES

Nanoparticles, lipsomes, phyto-complexes, ethosomes, etc. have been applied as drug delivery systems with great success and have greater potential for many more applications including, gene therapy, AIDS therapy, radiotherapy, delivery of proteins, antibiotics, virostatics and vaccines and as vesicles to pass the blood-brain barrier. The main focus lies on to improve their stability in biological environment, mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release and interaction with biological barriers. The cytotoxicity of nanoparticles (or other NDDS forms) or their degradation products is a major constraint so improvement in biocompatibility obviously is the main concern of future research. There are many technological challenges in developing the following techniques:

a) Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways;
b) Controllable release profiles, especially in case of sensitive drugs;
c) Materials for such NDDS that are biocompatible and biodegradable;
d) Architectures/ structures, such as biomimetic polymers, nanotubes, etc.;
e) Technologies for self-assembly;
f) Functional improvement (active drug targeting, on-command delivery, intelligent drug release devices/bio-responsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery);
g) Improve devices such as implantable devices/nanochips for nanoparticle release, or multi reservoir drug delivery-chips;

h) Nanoparticles for tissue engineering; e.g. for the delivery of cytokines to control cellular growth and differentiation, and stimulate regeneration or for coating implants with nanoparticles in biodegradable polymer layers for sustained release; and
i) Advanced polymeric carriers for the delivery of therapeutic peptide/proteins (biopharmaceutics)

To overcome these gaps the steps are needed to a) identify and isolate phyto-constituents which are compatible with various NDDS techniques, b) develop highly efficient and low cost NNDS techniques, c) formulate universal formulation schemes that can be used as intravenous, intramuscular or peroral drugs, d) develop better disease markers in terms of sensitivity and specificity, e) generate cell and gene targeting systems, f) device combined therapy and medical imaging, for example, nanoparticles for diagnosis and manipulation during surgery (e.g. thermotherapy with magnetic particles) and g) develop devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic nanoparticles that can correlate with the amount of ligand.

Epilogue: Medicinal plants are potential resource for anti-cancer compound. The antitumor activity of medicinal-plant-derived compounds may result from a number of mechanisms, including the effects on cytoskeleton proteins that play a key role in cell division, inhibition of DNA topoisomerase enzyme, antiprotease or antioxidant activity, stimulation of immune system, etc. From present review it has emerged that various herbal drugs have satisfactorily been evaluated for their pharmacokinetics both in animal and human models. However, they have suffered with six basic disadvantages like poor aqueous solubility (paclitaxel, quercetin, naringenin, silymarin, triptolide, artimisinins, *Cladonia substellata* and *Scutellaria baicalensis*), poor bioavailability (curcumin, quercetin, breviscapine, berberine, *Ginkgo biloba,* amelopsin and *Glycyrrhiza glabra*), short half-life (breviscapine), poor pharmaco-kinetic/slow pharmacological action (berberine, podophyllotoxin, artimisinins, *Salvia miltiorrhiza, Stephania tetrandra* and *Vaccinium myrtillus*), toxicity (triptolite and *Cathranthus roseus*) and poor physical stability (amelopsin and *Scutellaria baicalensis*). To overcome these constraints though derivative of a few herbal plants like Abraxane® and Taxol® of paclitaxel, and topotecan and irinotecan of camptothecin have been synthesized, yet their high cost and additional pharmacological attributes restricts their wide adaptability. *In vitro* studies of various products developed through novel drug delivery approaches reveal that they can satisfactorily resolve the major disadvantages associated with these herbal drugs. Among the novel drug delivery approaches nano-formulation have widely been exploited followed by liposome, ethosome and phyto-complex. However, integration of these approaches in complementary and alternative medicine is still in nascent stage. Presently we have only two marketed product i.e. Gingkgo select® from *G. biloba* and Mitroselect® from *V. myrtillus*. Thus, commercialization of these novel herbal products is prerequisite for green therapy of cancer.

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