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NANOTECHNOLOGICAL APPROACHES TO HERBAL DRUGS USED IN CANCER THERAPY

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ABSTRACT: In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are obtaining popularity both in developing and developed countries because of their natural origin and lesser side effects. Many traditional medicines in use and they are derived from medicinal plants, minerals and some organic matter. The World Health Organization (WHO) has listed 21,000 plants, which are useful for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world .This review focuses on herbal drug preparations of nanoformulation used in the treatment of different chronic diseases conditions in the world. This paper will discuss the benefits with use of herbal nanoformulation as Anti-cancerous activity. The application of nanotechnology is enhancement for the bioavailability and nanomization of herbal drugs like-nanocurcumin from *Curcuma longa*, nanovincristine from *Vinca rosea*, Podophylotoxin from *Podophylum hexendrum*, Taxol from Taxus plant etc. The nanocarriers have been made of safe materials, including synthetic biodegradable polymers, lipids and polysaccharides. Nanomedicines can be developed either as drug delivery systems or biologically active drug products. It is indicated that nanotechnology is one of the fastest developing of nanoformulation, the most potential and far-reaching high and new technology in current world. Nanoformulations is to increases the particles size and increase the surface area due to increases the bioavailability and reduces the side effect of herbal drugs and are useful for the treatment, diagnosis, monitoring and control of biological systems and have recently been referred to as nanomedicine.

INTRODUCTION: There are many traditional systems of medicine in the world, each with different associated ideas and cultural origins. Some of these, such as Tibetan traditional medicine, remain relatively localized in their country of origin; while others such as Ayurvedic and Chinese traditional medicines are increasingly used in many different areas of the world. This review will focus on the treatment of chronic diseases like cancer related to herbal traditional medicines.

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Ayurveda is the most widely practised of the Indian traditional medicine systems, but there are others such as Siddha and Unani which are also used in the Indian subcontinent [1]. The use of herbs for treating various disorders dates back several centuries.

Usually, herbal medicine are much safer and less toxicity than synthetic drugs has gained popularity in now a days and led to tremendous growth of phytopharmaceuticals usage. However, in now a days, data on evaluation of the therapeutic and toxic activity of herbal medicinal products became available. The advances in analytical technology have led to discovery of many new active constituents and an ever-increasing list of active constituents. Establishing the pharmacological basis for effectiveness of herbal medicinal products is a constant challenge. Of particular interest is the

question of bioavailability to determine what degree and how fast compounds are absorbed after administration of herbal medicinal products. Further interest is the elucidation of metabolic pathways (yielding potentially new active compounds), and the assessment of elimination routes and their kinetics. These data become an important issue to link data from pharmacological assays and clinical effects. Of interest are currently also interactions of herbal medicinal products with synthetically derived drug products.

A better understanding of the pharmacokinetics and bioavailability of phytopharmaceuticals can also help in designing rational dosage regimens [2]. Nanoformulation of herbal drugs possess many benefits, such as improving component solubility, enhancement of bioavailability, increasing absorbency of the organism, reducing medicinal herb doses, and achieving steady-state therapeutic levels of drugs over an extended period compared with traditional herbal drug preparations[3]. This review presents recent advances by nanotechnology of herbal drug in cancer therapy by enhancement of bioavailability and reduces the toxicity of the formulations.

Approaches of Nanotechnology:

In recent year, the nanonization of herbal medicines has attracted much attention [4]**,** there is some methods are used to prepared nanoformulation like Nanoparticles, nanoemulsions and liposome etc. are colloidal systems with particles varying in size from 10 nm to 1000 nm [5, 6].Nanoparticle systems with mean particle size well above the 100 nm standard have also been reported in literature, including nanonized curcuminoids [7], paclitaxel [8] and praziquantel [9] which have a mean particle size of 450, 147.7, and even higher than 200 nm, respectively.

1. Solid Lipid Nanoparticle (SLN):

It offers an alternative mechanism for drug delivery in comparison to other colloidal systems such as emulsions, liposomes & polymeric nanoparticles. It combines advantages of other colloidal systems while minimizing their drawbacks[10]. SLNs are easy to produce on a large scale by simple methods, offering better physicochemical stability & protection against degradation of labile drugs [11, 12, 13].Solid-lipid nanoparticles are produced from lipids which are solid at room temperature. The solid lipid is melted and the drug is incorporated into it. The whole system is stabilized by surfactant [14]. The matrix of the lipid particle formed is solid and therefore it can protect drug molecules against chemical degradation. Adding a liquid lipid (oil) to an oil/water emulsion containing a solid lipid, or mixture of solid lipids, promotes the formation of SLN[11]. Due to their small size (50–1,000 nm) and biocompatibility, SLNs may be used in the pharmaceutical field for various routes of administration, such as oral, parenteral, and percutaneous routes[13]. Polymeric nanoparticles offer some specific advantages over liposomes and nanoemulsion. For instance, the help to increase the stability of drug/proteins and useful controlled release properties[15].

2. Nanoemulsion:

It can be defined as thermodynamically stable isotropic system, containing transparent dispersions of oil and water stabilized by an interfacial film of surfactant molecule. Nanoemulsion droplets usually have the droplet size between 10 to 100 nm. Nanoemulsion droplets of both o/w as well as w/o types. The observed clearness of these systems is due to the fact that the maximum size of nanoemulsion droplets is less than one-fourth (25%) of the wavelength of visible light which is approximately 150 nm[16, 17, 18]. Nanoemulsions have a higher solubilization capacity than simple micellar solutions and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, because they can be manufactured with little energy input (heat or mixing) and has a long shelf life.

The nanosized droplet in nanoemulsion leads to increase in interfacial areas influencing the transport properties of the drug[19]. Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible [20, 21, 22, 23, 24].Due to their small droplet size, nanoemulsions possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of nanoemulsion breakdown. The main application of nanoemulsions is the preparation of nanoparticles

using a polymerizable monomer as the disperse phase (the so-called miniemulsion polymerization method) where nanoemulsion droplets act as nanoreactors. Another interesting application which is experiencing an active development is the use of nanoemulsionsas formulations, namely, for controlled drug delivery and targeting. The main application of nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase where nanoemulsion droplets act a nanoreactor [25].

3. Liposomes:

A liposome is a tiny bubble (vesicle), made out of the same material as a cell membrane. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases[26]. Liposomes are spherical, self-enclosed structures with a lipid bilayer (ranging from some nanometers to several micrometers) that possesses a unique amphiphilic character [27]. Silybin liposomal vesicles were prepared by ethanol injection method to evaluate its hepatoprotective and gastroprotective activity in mice against carbon tetrachloride induced hepatotoxicity. Result indicates 55 percent hepatoprotective activity by silymarin liposomes when compared to non-liposomal silymarin [28].

Silymarin proliposomes were prepared to assess its pharmacokinetic parameters and bioavailability in rats [29] and beagle dogs [30] after oral administration. The formulated silymarin had enhanced bioavailability when compared to pure silymarin. The hepatoprotective activity of silymarin was enhanced in albino rats by delivering its liposomal formulation through the buccal route [31]. Liposomal systems have been found to be useful and effective in targeting to liver cells. Galactosylated liposomes of silybin have ability to target to hepatocytes by attaching to lectin receptors present on the liver cells[32].

Similar investigations on silymarin were made to assess the pharmacokinetics & bioavailability in Wistar rats. Liposomes were prepared by film hydration method to evaluate its hepatoprotection activity. The formulation was found more efficacious than silymarin suspension in protecting the liver against paracetamol toxicity and the associated inflammatory conditions [33]. Some advantages of liposome are Provides selective passive targeting to tumor tissues (Liposomal doxorubicin), increased efficacy due to increased bioavailability and therapeutic index, increased stability via encapsulation, reduction in toxicity of the encapsulated agents, Site avoidance effect, Improved pharmacokinetic parameters (reduced limination, increased circulation life times), Flexibility to couple with site specific ligands to achieve active targeting [34].

Different types of herbal drugs used in Cancer therapy:

Cancer is an abnormal malignant growth of body tissue or cell. A cancerous growth is called a malignant tumor or malignancy. A non-cancerous growth is called benign tumor. The process of cancer metastasis is including of series of sequential interrelated steps, each of which is rate limiting. Plants are loaded with chemical with chemo protective activities of some of them are undergoing clinical trial is listed in (**Table 1**). Embarrassment of angiogenesis is a novel process of cancer therapy. The selected and careful use of this plant may definitely in anti-angiogenic therapy and thus in cancer management.

TABLE 1: LIST OF SOME HERBAL DRUGS USED IN CANCER THERAPY

S.No.	Common name	Botanical Name	Active Constituent	Part Used	Family	Reference
1.	Arjuna Bark	*Terminaliaarjuna*	Arjunolic acid, Arjunic acid	Bark	Combertacae	1, 35
2.	Kalmegh	*Andrographis Paniculata*	Andrographolide	Dried leaves	Acanthacae	1
3.	Vinca	*Catharanthus Roseus*	Vinblastine, Vincristine	Whole plant	Apocynacae	1
4.	Sambong	*Blumeabalsamifera*	Blumeatin, quercetin, rhamnetin	Leaves	Asteraceae	36
5.	May Apple	*Podophyllum Peltatum*	Podophyllotoxin, Quercetin	Dried Rhizome	Berberidacae	1,35

6.	Ginger	*Zingiber Officinalis*	Gingerol	Rhizome	Zingibaracae	[1, 35]
7.	Turmeric	*Curcuma longa*	Curcumin	Rhizome	Zingibaracae	[35]
8.	*Punarnava*	*Boerhaaviadiffusa L*	Punarnavine	Whole plant	Nyctaginacae	[36]
9.	Pomelo	*Citrus maxima*	Flavonoids, limonoids	Pulp	Rutaceae	[36]
10.	Amla	*Emblicaofficinalis*	Polyphenols, flavones, tannins	fruit	Euphorbiaceae	[36]
11.	Drumstick tree	*Moringaoleifera Lam*	Isothiocyanates	Whole plant	Moringaceae	[36]
12.	Indian trumpet tree	*Oroxylumindicum*	Baicalin, baicalein, Chrysin	Bark	Bignoniaceae	[36]
13.	Ginseng	*Panax Ginseng*	Ginsenosides, Polyacetyle	Root	Araliaceae	[1]
14.	Brazilian ginseng	*Pfaffiapaniculata*	Stigmasterol, sitosterol, allantoin,	Root	Amaranthaceae	[1]
15.	Onion	*Aliumcepa*	Disulfides, trisulfides, vinyl dithiins	Bulb	Liliaceae	[1]
16.	Indian Aloe	*Aloe barbadensis*	Aloin or barbaloin and Isobarbaloin	Leaves	Liliaceae	[1, 35]
17.	Senna	*Cassia senna*	Sennoside A, Sennoside B	Leaves	Caesalpinaceae	[1, 35]
18.	Lemon	*Citrus medica*	Citral, Limonene.	Root	Rutaceae	[1, 35]
19.	Mint	*Mimosa pudica*	Beta Carotene, Vitamin C	Whole plant	Mimosaceae	[1]
20.	Tobacco	*Nicotianatabacum*	Nicotine	Leaves	Solanaceae	[1]
21.	Indian Ipecac	*Tyloporaindica*	Emetine, Cephaeline	Root, Leaf	Asclepiadaceae	[1, 35]
22.	Pacific Yew	*TaxusBrevifolia*	Paclitaxel	Bark, Leaves	Taxaceae	[35]
23.	Cinchona	*Cinchona Officinalis*	Cinchonine	Bark	Rubiaceae	[35]
24.	Meadow Saffron Corm	*Colchicum Luteum*	Colchicine	Corm	Liliaceae	[35]
25.	Liquorice	*GlycyrrhizaGlabra*	Glycyrrhizine	Rhizome, Root	Fabaceae	[35]
26.	Pirorhiza	*PicrorhizaKurroa*	Picroside I, II, III	Rhizome, Root	Scrophulariaceae	[35]
27.	Rauwolfia	*RauwolfiaSerpentina*	Reserpine	Root	Apocynaceae	[35]

Innovative Approaches of Drug Discovery from Herbal Medicine:

Today, approximately 80% of immunosuppressive and anticancer drugs are of plant origin; their sales exceeded US$ 65 billion in 2003[37]. It is widely accepted that more than 80% of drug substances are either directly derived from natural products or developed from a natural compound [38]. And around 50% of pharmaceuticals companies are derived compounds first identified or isolated from herbs/plants, including organisms, animals, and insects, as active ingredients [39]. Drug discovery from herbs may be divided into three stages, namely, pre-drug stage, quasi-drug stage, and full-drug stage. They are described in detail in **Fig. 1.**

1. Pre-drug stage:

It has been assessed that approximately 420,000 plant species exist on earth, and the World Health Organization (WHO) estimates that herbal medicines provide primary healthcare for approximately 3.5 to 4 billion people worldwide, about 85% of traditional medicine involves the use of plant extracts[40], which may be called "modern herbal medicine." The Plants containing major active constituent of foodstuffs in humans have

formed the basis of various traditional medicine systems and conventional medicines that have been practiced for thousands of years during the course of human history. Until now, plants/herbs are still highly valued all over the world as a rich source of therapeutic agents for the cure and inhibition of various diseases and disorders; and about more than 35,000 plant species are used for medicinal purposes around the world [41, 42].

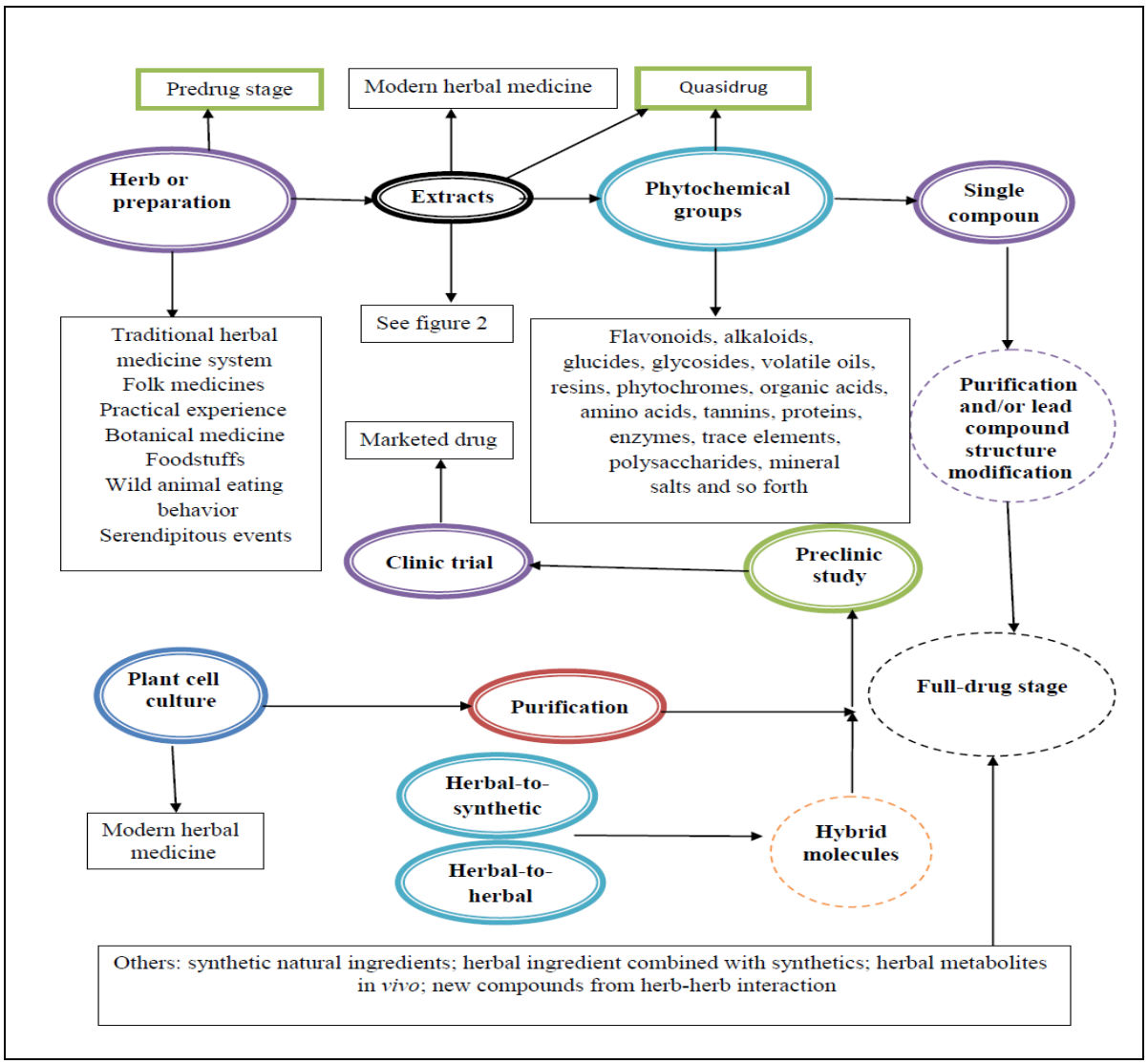

FIG. 1: INNOVATIVE APPROACHES OF DRUG DISCOVERY FROM HERBAL MEDICINE

In conventional Western medicine, 50–60% of pharmaceutical commodities containing natural products are synthesized from them; 10– 25%of all prescription drugs containing different active ingredients derived from plants [43]. It is well known that the medicinal value of herbs/plants depend on the presence of biological active ingredient(s) with drug-like properties. Recent investigation has identified a lot of biologically active substances/ingredients from both terrestrial and marine botanicals. For example, by 2007, 3, 563 extracts and 5,000 single compounds from 3,000 Traditional Herbal Medicines (THMs) have been composed in China [44]; the United States has screened about 114,000 extracts from an estimated 35,000 plant samples against a number of tumor systems as early as before the 1990s [45]. The examination for new drug from plant/herb has been rapidly increasing in recent few years, and it has led to the collection of an unusually diverse array of over 139,000 natural products [46].

All these compounds are likely useful for drug development. During the period 1981 to 2006, 47.1% of a total of 155 clinically approved

anticancer drugs were derived from nature in North America, Europe, and Japan market [47].

Herbs used in traditional or conventional medicines constitute only a small portion of naturally occurring plants. The advancement to different analytical methods and biological science, many bioactive chemical entities has been identified in plants or foodstuffs through phytochemical and pharmacological studies. Some examples, taxol (paclitaxel), an important anticancer drug, is isolated from the Pacific Yew tree [48]. Lycopene from tomatoes is thought to prevent certain types of cancers [49]. While humans have learned the technology of drug synthesis, plants remain a good source for drug discovery. As many popular drugs, such as paclitaxel, vincristine, vinblastine, artemisinin, camptothecin, and podophyllotoxin etc., were all derived from plants origin and developed by pharmaceutical companies.

Pre-drug stage comprises the information driven selection of herbs or plants in the first stage of drug discovery from herbs/plants.

2. Quasi-drug Stage:

Quasi-drug stage now in drug discovery from herbal medicine includes the preparation of extracts and phytochemical groups from herbs, including the discovery of lead compounds by using modern and conventional research tools. Phytochemical study of extracts of herbal preparations involves isolation, structure/composition elucidation, and bioactivity evaluation[50]. Herbs contain hundreds of active ingredients that may be useful for the development of therapeutic agents. Identification and isolation of phytochemical groups and/or single chemical entities from herbs or plants materials are essential for drug discovery.

It has been assessed that at least 15 major phytochemical groups in herbs (**Fig.2**); each group contains many individual chemical entities. For example, flavones include more than9, 000 known structures[51]. Alkaloids are an important class of active ingredient in herbs/plants, and more than10, 000 alkaloids have been isolated[52], of which more than 80 compounds have been clinically used, including camptothecin from Camptotheca acuminate, and vincristine from *Catharanthus roseus* for cancers therapy[53, 54].

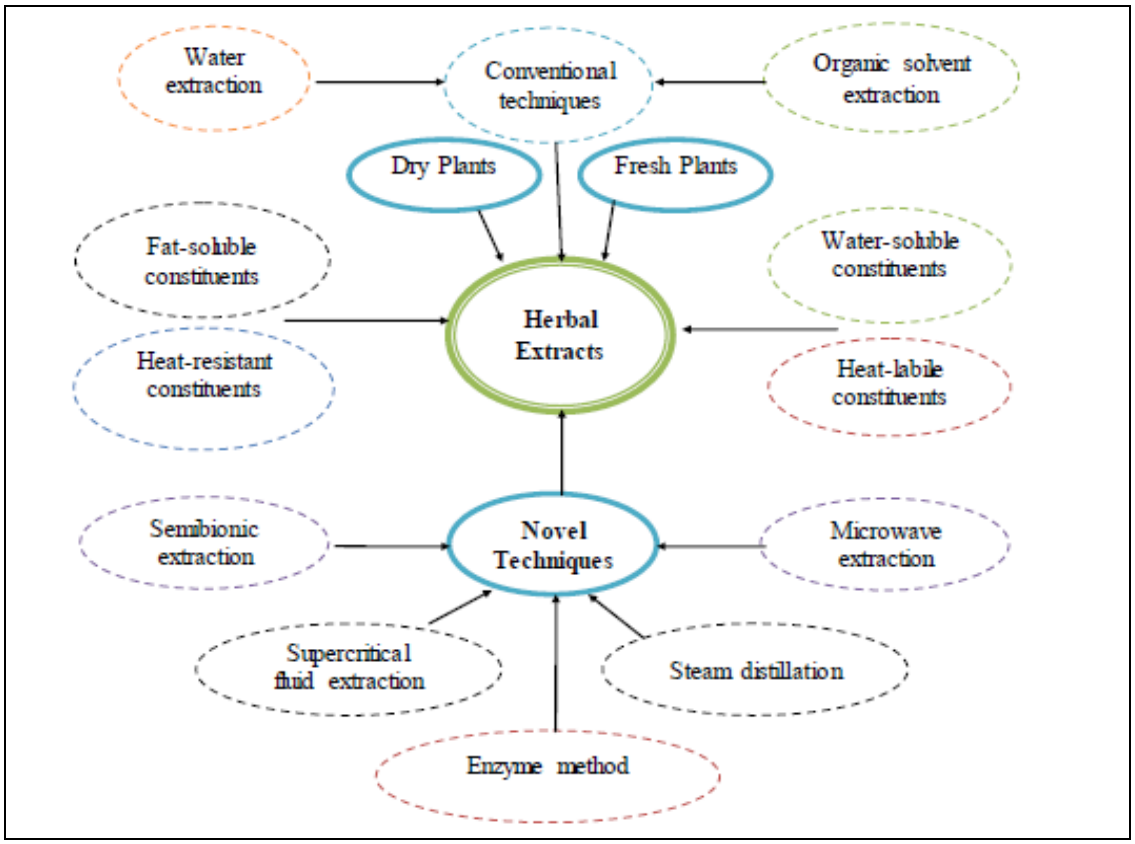

FIG. 2: NOVEL TECHNIQUES USED FOR EXTRACTION OF HERBAL PLANTS

The quasi-drug stage of drug discovery from herbal medicines is to examine for an active herbal ingredient or lead compound from herbs or plant materials for further drug development. It is well known that the prodrug design is a very inspiring mission for chemists in the synthesis of potential therapeutic agents.

3. Full-Drug Stage:

Today, drugs have become a daily essential for many people, especially the elderly with multiple health problems. In China, for example, there are 187,518 kinds of home-manufactured drugs, 8,492 kinds of imported drugs, and 1,489 patent-protected products of THM (Chinese patent medicine, Zhong-Cheng-Yao in Chinese) in the pharmaceutical market, and 8,409 drug candidates are now undergoing clinical trials [55]. In 2005 Chinese Pharmacopoeia, 582 herbal medicines are officially recognized and described and about 13,000 herbs and over 130,000 prescriptions currently used in various traditional medicines in China [56]. In USA, 2,900 chemical entities are currently under research and development, including agents to be used in the treatment of cancer therapy (750), [57].

The shortest method in drug discovery from herbal medicines is to isolate active ingredients from the natural plant source and this method is reasonable mainly depends on the concentration of the bioactive components, and some problems in purification, and the availability of the herb or plant; in particular whether the plant is a vulnerable species.

CONCLUSION: From this study, it is clear that the medicinal plants play a vital role against various diseases. Various herbal plants and plants extracts have significant Anti-cancerous activity in different animal models. Our review is concluded that the nanoformulation systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile herbal drugs into favorably bioavailable herbal drugs. Nanomized particles with small sizes are preferable because of a larger extent of bioactivity enhancement than that of nanomized particles with larger surface area and increases the particle size so that enhancement of bioavailability and solubility of herbal nanoformulation. Rapid advancements have been made in this area on improving the nano formulations of various chemopreventive agents such as curcumin, resveratrol, genistein, vincristine etc.

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