Journal of Materials and Environmental Science
ISSN : 2028-2508
CODEN : JMESCN

J. Mater. Environ. Sci., 2021, Volume 12, Issue 01, Page 01-14

http://www.jmaterenvironsci.com

Nanobiomedicine: A New Approach of Medicinal Plants and Their Therapeutic Modalities

Syed Muhammad Ali Shah [1], Zonaira Nisar [1], Jaweria Nisar [1], Muhammad Akram[1], Suresh Ghotekar [2, 3*], Rajeshwari Oza [3]

[1]*Department of Eastern Medicine, Government College University, Faisalabad, Pakistan*
[2]*Department of Chemistry, Sanjivani Arts, Commerce and Science College, Kopargaon 423 603, Savitribai Phule Pune University, Maharashtra, India*
[3]*Department of Chemistry, S.N. Arts, D.J.M. Commerce and B.N.S. Science College, Sangamner 422 605, Savitribai Phule Pune University, Maharashtra, India*

Received 09 Nov 2020,
Revised 11 Jan 2020,
Accepted 12 Jan 2021

Keywords
- ✓ Nanomedicines,
- ✓ Medicinal Plants,
- ✓ Infectious disease
- ✓ Nanoparticles.

ghotekarsuresh7@gmail.com
Phone: +918698255427

Abstract

The development of modern medicine launched as a remarkable innovation for humanity in the fight against many infectious diseases. Although, due to the large number of side effects associated with conventional medicine, people turned their attention again towards natural medicines which are human friendly with lesser or no side effects. Herbal medicines are being used from ancient times to cure infectious diseases and proved as potential alternatives. But, many of their practical uses are restricted due to their lower bioavailability and solubility. Plant based nanoparticles have been demonstrated are more effective alternatives; the combination of plant extract and nanoparticles was reported to increase the bioavailability and solubility of the herbal medicines so make their better usage. The objective of this review is to highlight the nanotechnology systems as an innovative drug delivery system in herbal medicines to enhance the therapeutic effects and bioavailability of naturally occurring drugs. In addition, the methods used to prepare herbal nanoparticle formulations, their structures and need of using herbs in combination with nanoparticles also addressed. It is presumed that this detailed review will be beneficial for subsequent applications in biomedical science and create the latest research opportunities. Data was collected from PubMed, Google scholar and Med line.

1. Introduction

From ages, human diseases are treated by herbal medicines in almost every infection. In modish age we have choice to make use of them instead of the synthetic ones as there are fewer side effects of traditional medicines [1-2]. Plants are natural source of treatment and are used from ages for food and medicine [3]. Indeed, natural medicines have grabbed the attention again instead of fighting in the number of infections. About 80% of the world population is now using herbal drugs for primary health care basically in developing countries [4]. But, these herbal therapies have some restrictions, due to stability issues and poor lipid solubility [5]. It is the first responsibility of the manufacturer of the herbal drugs to give sufficient stability for long-time storage and safe utilization by the patients. Mostly in traditional drugs, only a finite amount of administered amount gain access to the targeted site and most of the dose

get dispersed throughout the body depending on physiochemical and biochemical characteristics as a result giving low therapeutic effect [6-7]. As there is more than one active ingredient in herbal formulations, stability profiles of the herbal medicines should be determined. A stable phytoformulation will give more confidence to the patient [8]. Supply of active constituents has great significance in the efficacy of most of the species of plants having medicinal importance. Herbal medicinal extracts containing biologically active components, like tannins, flavonoids, and terpenoids, are tremendously miscible in water, but cannot cross the lipid membranes of the cells so have less absorption, also have extremely large molecular size, causing loss of bioavailability and effectiveness. Because of these drawbacks some extracts are not use in practice [9]. To conquer these problems, innovative systems of drug delivery has been developed for phytomedicines. These herbal innovative systems of drug delivery include vesicular delivery systems such as liposomes, ethosomes, phytosomes, transferosomes, and particulate delivery systems such as micropellets, microspheres, nanoparticles, and micro and nano emulsions. For the enhancement of stability, bioavailability and depletion of toxicity, many natural drugs have been assimilated into these drug delivery systems [10]. On the whole, herbal medicines are found in the market in the form of conventional dosage but now many strategies are developed these days to enhance their therapeutic effects and efficient delivery, inclusive of nanoparticles. In recent years, nanotechnology is significantly increased the usage of herbal medicines [11]. Amongst all the drug delivery systems, nanoparticles are thought-out to be an efficient drug delivery system [12]. It has been extensively recommended to blend the herbal drugs with nanotechnology. Nanostructured techniques are proving to be able to enhance the efficacy of herbal extracts also minimizing the required dose and side effects and enhancing activity. Nano technology can supply the active ingredients at an adequate concentration to the required site of action throughout the duration of treatment [9].

By 2015, the global business for nanotechnology based products is expected to meet US1trillion dollars. Nanotechnology also attracted the Chinese and Indian government to investigate and commit to it. About 20 million dollars are donated by Indian and Australian governments to initiate Australia-India Science Research Funding Programme. BCC Research published the report on the global value of the nanomedicines business in market which was 63.8 billion and 72.8 billion dollars in 2010 and 2011, correspondingly [13].

Different biological systems involve the preparation of nanoparticles, out of all these systems, nanoparticles biosynthesized from plants is suggested the highest appropriate technique. The whole process becomes environmental friendly by using plant substantial [14].

Nanotechnology is a significant cure to conquer the issues emerging regarding to herbal formulations. According to herbal drug researches, there are a number of benefits for herbal medicines as nano dosage forms have been developed. These advantages include enhancement of bioavailability, stability and solubility, impeding toxicity, improving biological activity and tissue macrophages dispensation, controlled delivery, inhibit the physical and chemical changes and disintegration [6]. Nano dosage form delivery systems is the best choice owing to their distinctive size and elevated carrying capabilities as they are seen to have more power to distribute the high amounts of drugs to the required sites [15].

Nanoparticles are diverse in size from 1-100 nanometers and consist of synthetic or natural polymer, alternate nanosized colloidal structures. The herbal medicine (Figure 1) is disbanded, captured, compacted or attached to nanoparticle structures. Nanoparticles can be prepared in nanocapsule or nanosphere forms depending upon their synthesis techniques. In nanocapsules, the drug is restricted to a hollow bounded by a distinctive polymer membrane. Whereas, in nano-spheres the drug is noticeably and homogeneously disseminated [16]. The nano-carriers are safe to use as they are prepared of harmless materials, comprising synthetic bio-decomposable polymers, polysaccharides and lipids [17].

Nanocarriers are nano-sized substances chiefly use as a carriage element for another material alike a drug. The most used nanocarriers are polymers, micelles, biological constituents, liposomes and other materials. Nanocarriers are presently utilized in drug delivery and their exceptional properties reveal prospective usage in chemotherapy. Various kinds of nano substances are being utilized in nanocarriers permits for hydrophobic and hydrophilic preparations to be distributed through the body [18]. As the most of the human body consists of water, the nanoparticles give the chief therapeutic effects to deliver the water insoluble drugs efficiently in humans. Depending upon the alignment of the phospholipids particles in micelles, they are able to hold both water soluble or insoluble drugs [19].

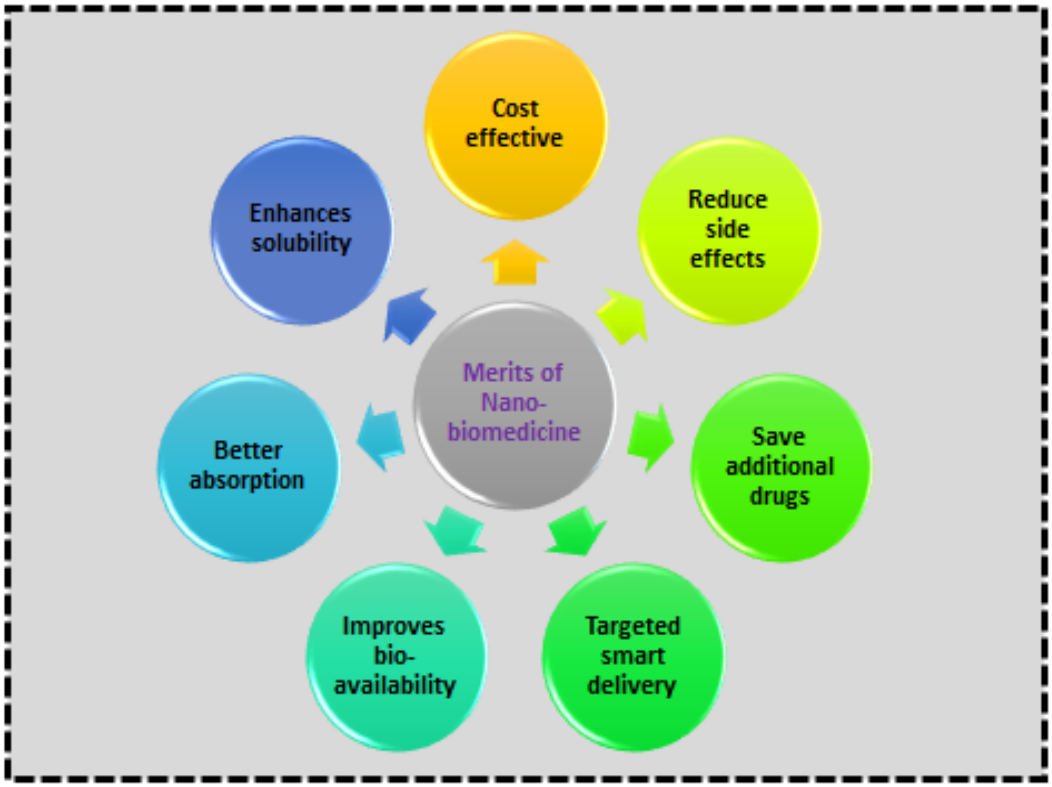

Figure 1: Merits of nanobiomedicines

2. Material and Methods Requirement of nanotechnology, an innovative drug delivery system for herbal medicines

Highly acidic pH of the stomach causing the drugs to be disintegrated into many components before gaining access to the blood and other components are reach to liver where they metabolized. As a result, the required amount of drug does not get into blood. If the required amount of the drug is not delivered to the site of action at 'lowest potential extent' then there will be no means to exhibit the therapeutic effect of the drug. Herbal nanomedicines (Figure 2) using carrier approaches reach their targeted site in appropriate amount by crossing all the hurdles such as stomach's acidic pH, metabolism of liver and enhance the circulation of the drug in to blood because of their small size [15, 20].

Nanodelivery system chooses the herbal medicines as it is practicable drug extrants for delivery through this system because of the following characteristics:

- Herbal extracts are accessible such as chloroform, petrol, acetone, and methanolic extracts but these are not appropriate to deliver as it is.
- The amount of the given drug is intended to be reduced as these are present in bulk forms. Currently marketed formulations lack target specificity for various chronic diseases.

- At present, herbal formulations available in market have some related side effects.
- Greater amounts of drug and lower efficacy with presently marketed formulations causing the patient's objections [21].

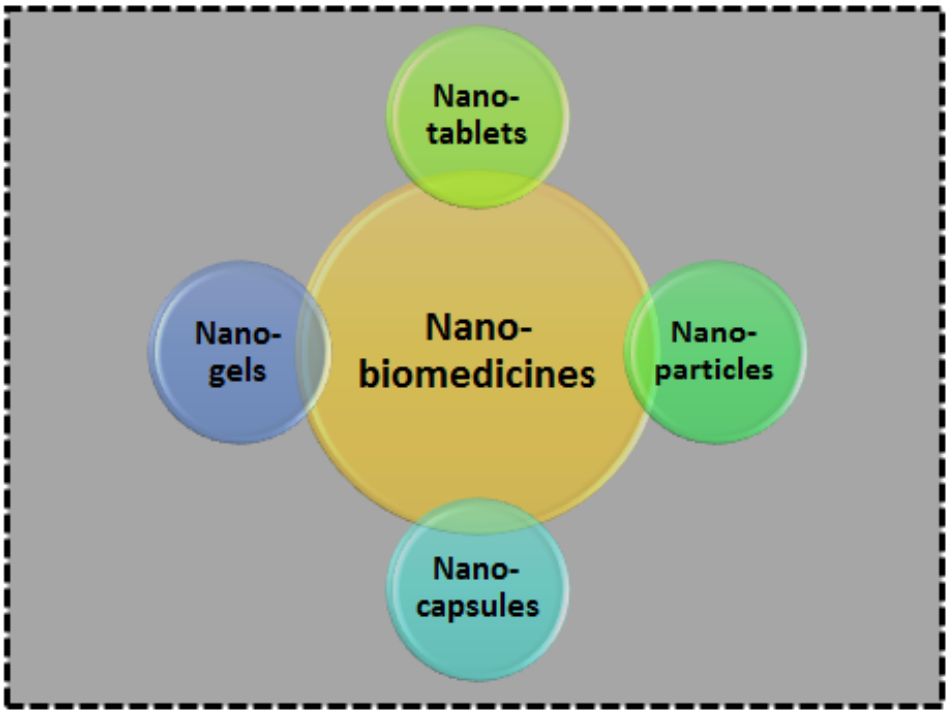

Figure 2: Types of herbal nanomedicines

3. Techniques for preparation of nanoparticles

For the synthesis of nanoparticles, many techniques have been evolved. These techniques are categorized into two chief classes depending upon the formulation needs either polymerization reaction or are accomplished right from a macromolecule or preformed polymer [22]. The polymerization technique is additionally categorized as emulsion and interfacial polymerization. Depending on continuous phase, emulsion polymerization is further classified as organic and aqueous polymerization. The synthesis of nanoparticles can also be done straight from already synthesized or natural polymers and by desolation of macromolecules. At present these polymeric structures have been synthesized by nebulization techniques [23].

3.1. Preparation and compression of drugs in polymeric nanoparticles

Polymeric nanoparticles are prepared (Figure 3) by using numerous approaches [23] depending upon the needs of its usage and a kind of drugs to be compacted. A large number of bioactive substances are being encapsulated by these nanoparticles and are broadly used to originate the nanomedicines. Biodecomposable polymeric nanoparticles are revealed as promising drug delivery system and extremely preferred. These types of nanoparticles offer precise/constant discharge characteristic, subcellular size and biocompatibility with tissue and cells [24]. Besides these, they are unchanging in blood, nonthrombogenic, non-virulent, noninflammatory, not susceptible to elicit an immune response, not causing activation of neutrophils, biodecomposable, don't have any action on reticuloendothelial system and appropriate to numerous particles such as medicines, proteins, nucleic acids or peptides [25].

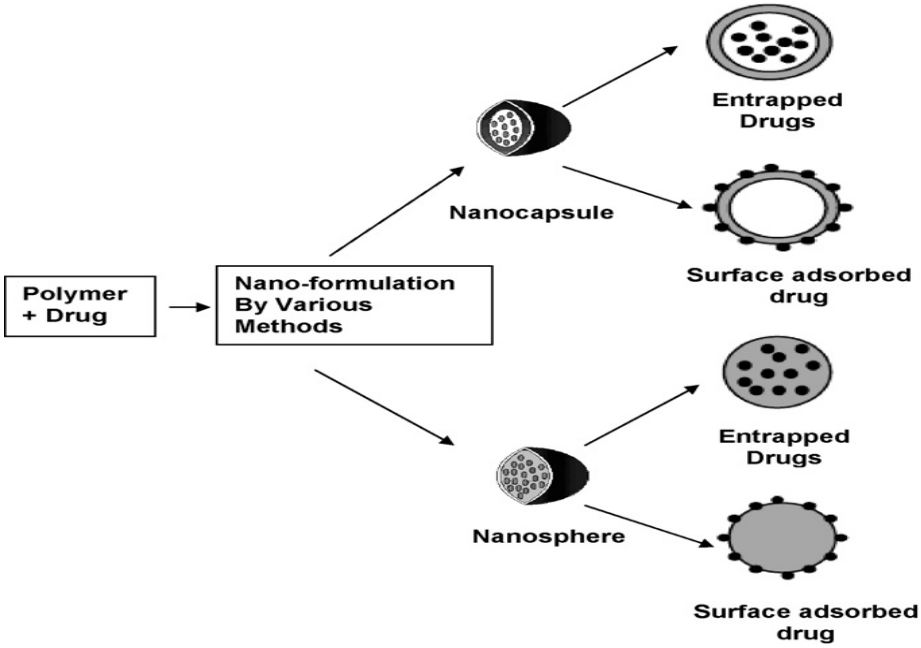

Figure 3: Forms of biodecomposable nanoparticles: Biodecomposable nanoparticles are categorized as nanocapsule, and nanosphere as stated to the physical organization. The drug particles are adapted one of the two paths either entangled inside or adsorbed externally on the surface [26].

3.2. Herbal nano tablets

The developing global populations with have no means to get clean water for drinking are now using herbal nanoparticles in the form of tablets for water purification. Brahmi (Bacopamonniera) extract is used to make these herbal nano tablets on a small porcelain disk packed with silver or copper nanoparticles that is positioned in a water vessel. Inside the water vessel it can frequently sanitize water for about six months. For precise and target specific delivery of drugs, nano tablets comprising of herbal medicines are used. Bhasmas layered nano herbal tablets are reported for the anticancer effects [27]. For making of energy drinks, nano coffee energy tablets are used effortlessly. The active constituents used in these drinks are vitamin C, Vitamin B6 B12 B5, niacin, Guarana seed extract, Folate, Chromium, caffeine (from herbal sources), glucuronolactone, Columbian baked coffee bean, Taurine, and leaf extracts of green tea [10]. A study was reported on the biological synthesis of silver nanoparticle using water base leaf extract of Piliostigma thonningii and applied in the sanitization of laboratory roused waste water.

4. Herbal medicines using nanotechnology formulations

Nano herbal drugs are synthesized from active phytocomponents or systemized extracts. Effectiveness and bioavailability of the delivered drug increases by using nanotechnology. Nano herbal formulations also reduce the side effects and verilency of the administered drugs [28].

4.1. Curcumin nanophytomedicine

Curcumin is a constituent of the turmeric (Curcuma longa), revealed many benefits regarding the treatment of various diseases. Many researches and experiments have showed the pharmacokinetics, protection, and effectiveness of this constituent in case of ailments in human body [29]. Curcumin is poorly soluble in water and highly soluble organic molecule which reducing its bioavailability. The metabolism of curcumin is so fast which causes further reduction in its bioavailability. All these issues have leading to find a superb-curcumin that gives all the advantages in a more precisely operational and bioavailable form. Small particles of curcumin compressed in oil hollow enclosed by sheath have

resolved this issue. Compression in these small particles causing the fat soluble curcumin to be absorbed better and also reveal the steady discharge into blood stream, increasing and exceeding bioavailability. Many experiments in vitro and on animals have proposed that curcumin have antioxidant, antitumour, antiarthritic and anti-inflammatory activity. Pharmacokinetic researches in vivo showed that curcumin entangled nanoparticles reveal about 09 fold rises in oral bioavailability in comparison of curcumin used with piperine as absorption stimulator [30].

4.2. Bhasma nanoparticles

Bhasma are exclusive preparation, dried with herbal juice or decoction and extensively suggested for curing of a many chronic disorders. Bhasma is defined as an ash attained after incineration; there is an extensive process of purification for the initial substance and then this substance will undergo reaction phase which includes amalgamation of certain other minerals and/or herbal extract. Bhasma has many significant effects on health such as sustaining optimal alkalinity for optimal health; reduce the destructive effects of acids that cause ailment. Bhasma breakdowns the heavy metals in the body and never produce detrimental metabolites as it does not metabolized [28].

Bhasma is the oldest form of nanotechnology. Bhasma is used from many years but extremely modern nanomedicine synthesized from metal after many systematic techniques to raw materials to convert them into active form. All these processes involve frequent incineration and crushing with certain herbal juice and other definite drug. Its basic properties changed due to its tiny size. The size of the particle is 56 nm when assessed by different tools and methods such as AFM (atomic force microscope) and scaning electron microscope [27].

4.3. Nanoparticles of Aloe vera extract

Many creams or gels extensively use the aloe vera extract in its formulations for the care of skin. The creams or lotion preparations use for dermatitis, dryness, psoriasis, scaling, flaking, eczema, sunscreen and antiaging contain aloe vera extracts mostly. The present researches on Aloe vera extract in Japan suggested that it is not able to cross the stratum cornium. There is an obstacle for aloe vera extract to penetrate the skin, as aloe vera is hydrophilic compound and stratum cornium consists of high protein cells and intracellular lipid domain which act as impermeable barrier for it. For resolving this issue dose of the extract to skin increases but it causes inflammation. This study explored liposome comprising Aloe vera from soybean lecithin that increases the penetrating power of extract. In vitro, human skin fibroblast and epidermal keratinocytes used for revealing the penetration power of prepared Aloe vera comprising liposome. They have diameter <200 nm. The research suggested that the rate of proliferation is dramatically higher after using liposome comprising Aloe vera than without encapsulation. Moreover, the synthesis of collagenase also enhanced by 23% with liposomal aloe vera extract in comparison to 4% without encapsulation extracts [31].

4.4. Tanshinone IIA nanoparticles

Tanshinone IIA (TA) is a chief active constituent of Danshen (Salvia miltiorrhiza), a famous ancient Chinese medicine. Due to its lesser solubility in water and inadequate suspension, most of the therapeutic effects are restricted. To overcome this issue, TA nanoemulsions are prepared. Two prime preparations of TA nanoemulsions were formulated and both showed remarkably increased release capacity in vitro in comparison to TA alone. The comparison between TA alone and TA nanoemulsions showed that there is 103.4-fold enhanced cytotoxicity against T24 human bladder cancer cells by using TA nanoemulsions depending on dose and time [32].

4.5. Artemissia annua nanocapsules

Artemissia annua is the herb of the Asteraceae family, having a single stem and cultivated annually, the active constituent is Artemisinin [33]. Its therapeutic actions include powerful antimalarial activity. Its clinical applications are confining to its lower pharmacokinetic characteristics and lesser halflife. The nanotechnology solved this issue by making the nano-covered artemisinin. These are present in nanocapsules form and distributed more precisely in aqueous solutions. The artemisinin nanocapsules showed enhanced hydrophilic activity than the artemisinin alone [34]. These preparations also cause constant discharge of drug and showed anticancer activity [35].

4.6. Berberine nanomedicine

Berberine is naturally found isoquinoline alkaloid. A number of medicinal plants have this alkaloid in different parts such as roots, rhizome, and stem bark. Berberine has incredible potency to treat many physiological ailments [36]. Many researches revealed that berberine has marvelous antiinflammatory and anticancerous activity [37]. Berberine reported remarkable inhibitory and killing activity on human malignant brain tumor, cancer of esophagus, human leukemia and colon cancer cells [38]. Hence there are many therapeutic effects of berberine was reported so it was suggested to make its nanoparticles after encapsulation to ease the drug delivery [39].

4.7. Centella asiatica nanoparticles

Centella asiatica (L.) famous as "Gotu Kola" is potential brain tonic in natural medicines. Its acts by different methods like inbiting the enzymes, comprehensive neuroprotection by different modes of action such as enzyme inhibition, inhibition of amyloid plaque establishment in Alzheimer's disease, reducing the toxicity of dopamine in Parkinson's disease, and diminishing oxidative stress. Thus this is the recommended emerging natural medicine with required neuroprotective potency [40]. Silver nanoparticles were synthesized from in vitro derived callus extracts of C. asiatica (L.) (Figure 4), callus obtained from the extract of its leaf. These nanoparticles showed tremendous antibacterial property [41]. Many researchers reported that C. asiatica (L.) has various types of therapeutic actions like it showed anxiolytic activity [42], anti- nervousness [43], and antioxidant [44]. Moreover, it is also recommended in the cure of leprosy, wounds, cancer, fever, allergy and syphilis [45]. There are significant biological properties of C. asiatica extract but its practical use is restricted because it is unstable physically. Extract in the form of powder show greater hygroscopic properties. To prevent it from external humidity, there was a need to develop the nanoparticles in which the extract is captured inside. Chitosan-alginate nanoparticles of C. asiatica extract were synthesized by ionic gelation method. These formulations provided physical stability to C. asiatica than its extract alone [46].

4.8. Celastrol nanoparticles

Celastrol, tripterine is obtained from the root extract of Trypterygium wilfordii Hook F reveals significant importance for the cure of autoimmune syndromes [47]. The family of Trypterygium wilfordii Hook F is Celastraceae. It is also called as the 'Thunder of God Vine' and from many years used in ancient chinese remedies for the cure of rheumatoid arthritis [48]. Further, therapeutic uses of celastrol confines to its lesser water solubility. Celastrol nanoparticles are prepared and their antitumor activity was tested in vitro which reveals that celastrol nanoparticles remarkably prevent the propagation of human retinoblastoma cells depending upon dose and time. They cause apoptosis in targeted cells and prevent the growth of retinoblastoma in a xenograft mouse model which proves it an significant substitute for the cure of retinoblastoma [49].

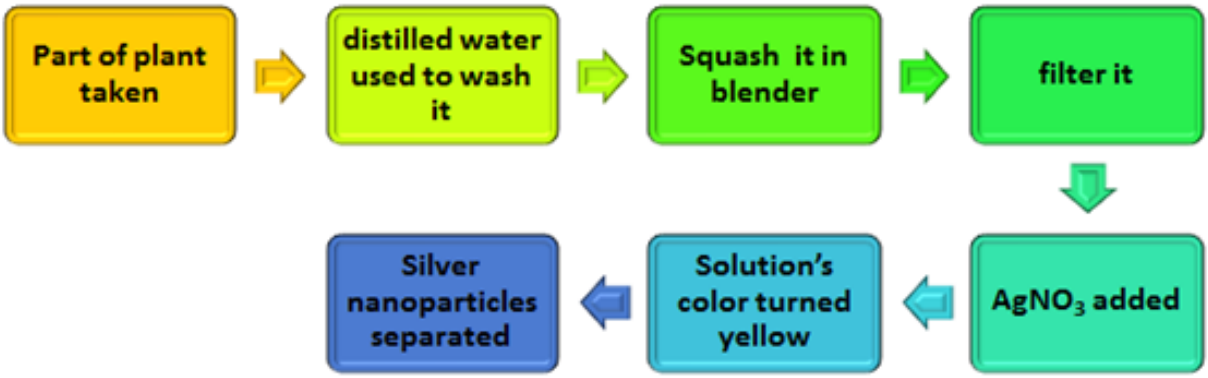

Figure 4: Process of in vitro synthesis of silver nanoparticles from different parts of the plant

4.9. Murva nanoparticles

Maerua oblongifolia from family Capparaceae comprises of many bioactive constituents. Murva, one of the effective phytochemical attained from Maerua oblongifolia has been conventionally used in the treatment of numerous disorders [50]. It is reported that murva has significant potency to cure the disorder such as anaemia, fever, stomach disorders, diabetes, typhoid, UTIs and cough [51]. However, it has lesser water solubility and lower bioavailability which restricts its practical uses. Consequently, it is prepared as nanoparticles to enhance its solubility and bioavailability [19]. Various methods are suggested to enhance the stability and bioavailability of the naturally occurring plant drugs. Out of all these methods, nano substances based drug delivery systems gained more importance and modern favorable mechanism. Murva is formulated with chitosan nanoparticles using ionic gelation method, particle size of these nanoparticles is lesser than 650 nm. In vitro study shows that these nano preparations presented moderate and steady discharge. These nano preparations were reported as an efficient system for oral steady use of murva and also boost up its and bioavailability [19].

4.10. Genistein nanoparticles

Genistein, isoflavone was extracted from dried foodstuffs [52] is a chief active constituent of soyabean, scoparius and other leguminous plants. It is a phytoestrogen [53] and antioxidant [54]. It also showed the potential to reduce the chances of osteoporosis, heart disorders, breast and uterine carcinomas [55]. However, it has lesser bioavailability and water solubility which reduces its practical usages [56]. Hence there was a need to synthesize the genistein nanoparticles to enhance its water solubility and bioavailability. Genistein nanoparticles were prepared by using nano-precipitation technique [57]. Research revealed that genistein comprising nanoparticles have greater (241.8%) comparative bioavailability than the genistein alone [58].

4.11. Danshen (Salvia miltiorrhiza) nanoparticles

Danshen (Salvia miltiorrhiza), a conventional chinese drug, has potential applications in the remedies for coronary heart disease [59]. It is a dried root of Salvia miltiorrhiza, a plant of Lamiaceae family. It is extensively used as remedies for stimulating circulation and curing blood stasis. Danshen has wide applications in the curing of coronary cardiovascular disease, cerebrovascular disorders and hyperlipidemia [60-61]. However, in addition to have such a marvelous benefit, this natural drug has a chief disadvantage of slow pharmacological activity. Salvia miltiorrhiza nanoparticles show greater antioxidant activity and the discharge was quicker than the conventionally powered drugs [62].

Phospholipids complex laden nanoparticles similarly showed greater oral bioavailability than the traditional samples [63].

4.12. Cuscuta nanoparticles

Cuscuta reflexa is the plant of family Convolvulaceae, a parasitic plant; generally recognized as dodder plant, amarbel, akashabela. Conventionally it is termed as miracle plant [64]. Flavanoids and lignins are the chief components of this plant. It possesses anticancerous [65], antiaging [66] and immune-stimulatory properties [67]. Due to its lower water solubility its oral administration is restricted. Nanoparticles of Cuscutta chinensis have been prepared by nano precipitation method [68]. C. chinensis, one more species of Cuscuta is present with the similar name in the native marketplaces and is a well-known adulterant of the actual herbal drug, C. reflexa [69]. Nanoparticles of C. chinensis display greater hepatoprotective and antioxidant properties at lesser concentration than the extract alone [12].

4.13. Quercetin nanoparticles

Quercetin, a flavonoid expelled from air dried plant part (primarily from bark and leaf) of Spohora japonica L. belongs to family Fabaceae. Quercetin has greater antioxidant activity than eminent antioxidants like ascorbyl and trolox [70]. Besides this, it exhibits anticancerous and antiviral properties [71]. Dispite the large number of pharmacological characteristics, its applications in biomedical field is restricted due to its lesser water solubility and stability which leads to poor bioavailability [72]. Quercitin comibines with superparamagnetic iron oxide nanoparticle (SPION) are proved to increase the bioavailability of quercetin. The study was suggested that these nanoparticles bind to specific proteins causing prevention of neural cell apoptosis and increases learning and memory. Hence, SPIONs might enhance the bioavailability of quercetin and increase learning and memory [73].

4.14. Paclitaxel nanoparticles

Paclitaxel is one of the active constituent of the plant Taxus brevifolia Nutt. obtained from its bark. This plant belongs to the family taxaceae has anticancerous properties. Its greater lattice energy consequences in inadequate water solubility (0.7-30 µg/ml-1) restricted its effectiveness [74]. Accordingly integration of paclitaxel into nanoparticles improved its anti-tumoral activity [75]. Paclitaxel laden nanoparticles were synthesized by nano-precipitation method [76] and by sequential simplex optimization method [77]. Paclitaxel nanoparticles improve drug stability, maintain the steady drug discharge and increase bioavailability [12].

5. Conclusion

Nanoparticles play a vital role to combat the issues associated with herbal medicines i.e. lower bioavailability and lesser water solubility. There are many researches being conducted everywhere in the world on the herbal medicines and remedies. In addition, associated drawbacks of herbal drugs have also been studied. Many systems are derived to overcome these issues, among all the systems, nanotechnology gives promising results. It increases the bioavailability, stability and water solubility of the herbal medicines. Certainly, nano-phytomedicines have showed remarkable activities to treat the diseases and enhance the therapeutic efficacy of herbal medicines. All of the nano-phytomedicines discussed above have demonstrated the significantly enhanced efficacies. They are increasing the therapeutic applications of many herbal drugs, also reducing the therapeutic dose of herbal medicines; hence the side effects of large dosages are also minimized.

Nano-phytomedicines provide many banefits: 1) Enhance water or lipid stability and solubility; 2) Improved membrane crossing ability; 3) Transcytosis across tight epithelial barriers; 4) Two or more phytomedicines can deliver simultaneously; 4) Combination therapy provides enhanced clinical benefits; 5) Increase intracellular delivery of macromolecule phytomedicine; 6) Target specific drug delivery to cells/tissue 7) Slow and steady delivery 8) Increase bioavailability and pharmacological properties 9) Enhance mucoadhesion 10) prevention from disintegration or virulency 11) Dispersion of tissue macrophages improved 12) Monitoring of sites of drug delivery through imaging modalities.

6. Future perspectives

Many herbal drugs have anti-cancerous properties; nanoparticle formulations already have grabbed the attention of many researchers. However, more researches are needed in the field of nano-phytomedicines so it could facilitate in cancer therapy. The herbal medicines also have high antioxidant effects and many health benefits. The researches on the combination of traditional medicines and modern nanotechnology will give more potential alternatives in the pharmaceutical field and improve the health of the mankind. Further researches are needed to highlight the physicochemical, biological, and pharmacotoxicological properties of these nano-phytomedicines so that to originate the safe and more reliable products. The combination of nanoparticles and medicinal plants might be an effective therapeutic choice to fight against many diseases and demonstrate a game changer in the field of nanomedicine. The nano-phytomedicines will perform a future generation remedies to alleviate the threat of side effects. Revolutionary research, continuous attempts, a huge number of practices, and the marketing of nano-phytomedicines will certainly give upgrade status of life.

References

1. F. Alexis, P. Basto, E. Levy-Nissenbaum, A.F. Radovic-Moreno, L. Zhang, E. Pridgen, O.C. Farokhzad, HER-2-Targeted Nanoparticle-Affibody Bioconjugates for Cancer Therapy, *Chem Med Chem: Chem. Ena. Drug Disco.*, 3(12) (2008) 1839-1843.
2. L.R. Atmakuri, S. Dathi, Current trends in herbal medicines, *J. Pharm. Res.*, 3(1) (2010) 109-113.
3. S.G. Bhokare, C.C. Dongaonkar, S.V. Lahane, P.B. Salunke, V.S Sawale, M.S. Thombare, Herbal Novel Drug Deliver: A Review, *World J. Pharm. Pharma. Sci.*, 5(8) (2016) 593-611.
4. B. Goldberg, Alternative medicine: The definitive guide future medicine, *Washington: Puyallup*, (1994) 257.
5. G.T. Kulkarni, Herbal drug delivery systems: An emerging area in herbal drug research, *J. Chrono. Drug Deli.*, 2(3) (2011) 113-119.
6. R. Sharma, J. Hazra, P.K. Prajapati, Nanophytomedicines: A Novel Approach to Improve Drug Delivery and Pharmacokinetics of Herbal Medicine, *Bio. Bull.*, 3(1) (2017) 132-135.
7. K. Kumar, A.K. Rai, Miraculous therapeutic effects of herbal drugs using novel drug delivery systems, *Inter. Res. J. Pharm.*, 3(2) (2012) 27-30.
8. L. Thakur, U. Ghodasra, N. Patel, M. Dabhi, Novel approaches for stability improvement in natural medicines, *Pharmaco. Revi.* 5(9) (2011) 48.
9. P.B. da Silva, R. dos Santos, M. Aparecido, B.V. Bonifácio, K.M.S. Negri, M.R. Sato, M. Chorilli, Nanotechnological strategies for vaginal administration of drug-A review, *J. Biomed. Nanotech.*, 10(9) (2014) 2218-2243.

10. S.K. Nune, N. Chanda, R. Shukla, K. Katti, R.R. Kulkarni, S. Thilakavathy, K.V. Katti, Green nanotechnology from tea: phytochemicals in tea as building blocks for production of biocompatible gold nanoparticles, *J. Mater. Chem.*, 19(19) (2009) 2912-2920.
11. G.G. Tapadiya, Impact of nanotechnology on global trade of herbal drugs: An overview, *Inter. J. Green Pharm.*, 11(03) (2017).
12. N. Arulanandraj, S. Dhivya, V. Gopal, A review on Herbal Nanoparticles, *Pharma Tutor,* 6(5) (2018) 32-37.
13. A.N. Sahu, Nanotechnology in herbal medicines and cosmetics, *Inter. J. Res. Ayur. Pharm.*, 4(3) (2013) 472-474.
14. S. Ghotekar, A review on plant extract mediated biogenic synthesis of CdO nanoparticles and their recent applications, *Asian J. Green Chem.*, 3(2) (2019) 187-200.
15. N.K. Bairwa, N.K. Sethiya, S.H. Mishra, Protective effect of stem bark of Ceiba pentandra Linn. against paracetamol-induced hepatotoxicity in rats, *Pharmaco. Res.*, 2(1) (2010) 26.
16. D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, Nanocarriers as an emerging platform for cancer therapy, *Nat. Nanotech.*, 2(12) (2007) 751.
17. M. Singh, S. Manikandan, A.K. Kumaraguru, Nanoparticles: a new technology with wide applications, *Res. J. Nanosci. Nanotech.*, 1(1) (2011) 1-11.
18. V.K. Gupta, P.K. Karar, S. Ramesh, S.P. Misra, A. Gupta, Nanoparticle formulation for hydrophilic & hydrophobic drugs, *Inter. J. Res. Pharma. Sci.*, 1(2) (2010) 163-169.
19. N. Arulanandraj, V. Gopal, S. Dhivya, G. Jayabalan, Nanotechnological approach to enhance the stability and bioavailability of the herbal drug" murva", *J. Drug Deli. Thera.*, 8(5) (2018) 251-256.
20. D. Yadav, S. Suri, A.A. Choudhary, M. Sikender, B.N. Hemant, N.M. Beg, Novel approach: Herbal remedies and natural products in pharmaceutical science as nano drug delivery systems, *Int. J. Pharm. Tech.*, 3(3) (2011), 3092-3116.
21. S.H. Ansari, M. Farha Islam, Influence of nanotechnology on herbal drugs: A Review, *J. Pharma. Tech. Res.*, *3*(3) (2012) 142.
22. P. Couvreur, C. Dubernet, F. Puisieux, Controlled drug delivery with nanoparticles: current possibilities and future trends, *Euro. J. Pharma. Biopharma.*, 41(1) (1995) 2-13.
23. C.P. Reis, R.J. Neufeld, A.J. Ribeiro, F. Veiga, Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles, *Nanomed.: Nanotech., Bio. Medi.*, 2(1) (2006) 8-21.
24. J. Panyam, V. Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue, *Adv. Drug Deli. Revi.* 64 (2012) 61-71.
25. A. des Rieux, V. Fievez, M. Garinot, Y.J. Schneider, V. Préat, Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach, *J. Contro. Rele.*, 116(1) (2006) 1-27.
26. W.Tiyaboonchai, Chitosan nanoparticles: a promising system for drug delivery, *Nare. Uni. J.: Sci. Tech. (NUJST)*, 11(3) (2013)51-66.
27. P.K. Sarkar, A.K. Chaudhary, Ayurvedic Bhasma: the most ancient application of nanomedicine, 69 (2010) 901-905.
28. D. Pal, C.K. Sahu, A. Haldar, Bhasma: the ancient Indian nanomedicine, *J. adv. Pharm. Tech. Res.,* 5(1) (2014) 4.
29. S.C. Gupta, S. Patchva, B.B. Aggarwal, Therapeutic roles of curcumin: lessons learned from clinical trials, *The AAPS J.*, 15(1) (2013) 195-218.

30. P. Anand, S.G. Thomas, A.B. Kunnumakkara, C. Sundaram, K.B. Harikumar, B. Sung, B.B. Aggarwal, Biological activities of curcumin and its analogues (Congeners) made by man and mother nature, *Biochem. Pharmacol.*, 76(11) (2008) 1590-1611.
31. M. Takahashi, D. Kitamoto, Y. Asikin, K. Takara, K. Wada, Liposomes encapsulating Aloe vera leaf gel extract significantly enhance proliferation and collagen synthesis in human skin cell lines, *J. Oleo Sci.*, 58(12) (2009) 643-650.
32. L.C. Chang, C.L. Wu, C.W. Liu, W.H. Chuo, P.C. Li, T.R. Tsai, Preparation, characterization and cytotoxicity evaluation of tanshinone IIA nanoemulsions. *J. Biomed. Nanotech.*, 7(4) (2011) 558-567.
33. Y. Chen, X. Lin, H. Park, R. Greever, Study of artemisinin nanocapsules as anticancer drug delivery systems, *Nanomed.: Nanotech., Bio. Med.*, 5(3) (2009) 316-322.
34. G.V. Sathyavathi, A.K. Gupta, N. Tandon, Medicinal Plants of India, New Delhi (India), Indian Council of Medical Research, 2 (1989) 230-239.
35. C. Youfang, L. Xianfu, P. Hyunjin, G. Richard, Artemisnin nanoparticles, *Nanomed. Nanotechnol. Biol. Med.*, 5 (2009) 316-322.
36. I.P. Singh, S. Mahajan, Berberine and its derivatives: a patent review (2009–2012), *Exp. Opin. Thera. Pate.*, 23(2) (2013) 215-231.
37. K. Fukuda, Y. Hibiya, M. Mutoh, M., Koshiji, S. Akao, H. Fujiwara, Inhibition of activator protein 1 activity by berberine in human hepatoma cells, *Planta Medica*, 65(04) (1999) 381-383.
38. I. Bala, S. Hariharan, M.R. Kumar, PLGA nanoparticles in drug delivery: the state of the art, *Criti. Rev.™ in Thera. Drug Carr. Sys.*, 21(5) (2004) 387-422.
39. M. Khemani, M. Sharon, M. Sharon, Encapsulation of berberine in nano-sized PLGA synthesized by emulsification method, *ISRN Nanotech.*, 2012 (2012).
40. I.E. Orhan, Centella asiatica (L.) Urban: from traditional medicine to modern medicine with neuroprotective potential, *Evidence-based Comple. Alter. Medi.*, 2012 (2012).
41. S. Thakur, S. Thakur, M. Shandilya, R. Rai, Synthesis of silver nanoparticles from centella asiatica (L) plant and in vitro derived callus culture: Assessment of antibacterial activity, *Acad. J. Biotech*., 6(6) (2018) 066-073.
42. J. Bradwejn, Y. Zhou, D. Koszycki, J. Shlik, A double-blind, placebo-controlled study on the effects of Gotu Kola (Centella asiatica) on acoustic startle response in healthy subjects, *J. Clin. Psychopharm.*, 20(6) (2000) 680-684.
43. R.D. Lucia, Pharmacological and toxicological studies on Centella asiatica, *Fitoterapia*, 68,1997, 413-416.
44. H. Meena, H.K. Pandey, P. Pandey, M.C. Arya, Z. Ahmed, Evaluation of antioxidant activity of two important memory enhancing medicinal plants Baccopa monnieri and Centella asiatica, *Ind. J. Pharmacol.*, *44*(1) (2012) 114.
45. B.E. Van Wyk, B.V. Oudtshoorn, N.Gericke, Medicinal Plants of South Africa, *Briza*, (1997).
46. S. Okonogi, J. Sirithunyalug, Y. Chen, Nanoencapsulation of Centella asiatica bioactive extract, In *XVIth International Conference on Bioencapsulation, Dublin, Ireland*, 2008.
47. H. Li, Y.Y. Zhang, H.W. Tan, Y.F. Jia, D. Li, Therapeutic effect of tripterine on adjuvant arthritis in rats, *J. Ethnopharmacol.*, 118(3) (2008) 479-484.
48. X. Tao, J.J. Cush, M.I.T.Z.I. Garret, P.E. Lipsky, A phase I study of ethyl acetate extract of the chinese antirheumatic herb Tripterygium wilfordii hook F in rheumatoid arthritis, *The J. Rheuma.*, 28(10) (2001) 2160-2167.

49. Z. Li, X. Wu, J. Li, L. Yao, L. Sun, Y. Shi, Y. Li, Antitumor activity of celastrol nanoparticles in a xenograft retinoblastoma tumor model, *Inter. J. Nanomed.*, 7 (2012) 2389.
50. K. Madhava Chetty, K. Sivaji, K. Tulasi Rao, Flowering Plants of Chittoor District, Andhra Pradesh, India, *Published by Students Offset Printers, Tirupati*, 490 (2008) 34-35.
51. N. Kumar, A.K. Singh, Plant profile, phytochemistry and pharmacology of Avartani (Helicteres isora Linn.): A review, *Asi. Pac. J. Trop. Biomed.*, 4 (2014) S22-S26.
52. J. Liggins, A. Mulligan, S. Runswick, S.A. Bingham, Daidzein and genistein content of cereals, *Euro. J. Clini. Nutri.*, 56(10) (2002) 961.
53. A. Rusin, Z. Krawczyk, G. Grynkiewicz, A. Gogler, J. Zawisza-Puchałka, W. Szeja, Synthetic derivatives of genistein, their properties and possible applications, *Acta Biochi. Polo.*, 57(1) (2010) 23-34.
54. C.A. Lamartiniere, W.B. Murrill, P.A. Manzolillo, J.X. Zhang, S Barnes, X. Zhang, N.M. Brown, Genistein alters the ontogeny of mammary gland development and protects against chemically-induced mammary cancer in rats, *Proce. Soc. Experi. Bio. Medi.*, 217(3) (1998) 358-364.
55. N. Behloul, G. Wu, Genistein: a promising therapeutic agent for obesity and diabetes treatment, *Euro. J. Pharmacol.*, 698(1-3) (2013) 31-38.
56. A. Cassidy, P. Albertazzi, I.L. Nielsen, W. Hall, G. Williamson, I. Tetens, C. Steiner, Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women, *Procee. Nutri. Soc.*, 65(1) (2006) 76-92.
57. L.M. Andrade, C. de Fátima Reis, L. Maione-Silva, J.L.V. Anjos, A. Alonso, R.C. Serpa, S.F. Taveira, Impact of lipid dynamic behavior on physical stability, in vitro release and skin permeation of genistein-loaded lipid nanoparticles, *Euro. J. Pharm. Biopharm.*, 88(1) (2014) 40-47.
58. J. Tang, N. Xu, H. Ji, H. Liu, Z. Wang, L. Wu, Eudragit nanoparticles containing genistein: formulation, development, and bioavailability assessment, *Inter. J. Nanomed.*, 6 (2011) 2429.
59. J. Luo, W. Song, G. Yang, H. Xu, K. Chen, Compound Danshen (Salvia miltiorrhiza) dripping pill for coronary heart disease: an overview of systematic reviews, *The Amer. J. Chin. Medi.*, 43(01) (2015) 25-43.
60. L. Zhou, M. Chow, Z. Zuo, Improved quality control method for Danshen products-consideration of both hydrophilic and lipophilic active components, *J. Pharma. Biomed. Ana.*, 41(3) (2006) 744-750.
61. D.G. Kang, H. Oh, E.J. Sohn, T.Y. Hur, K.C. Lee, K.J. Kim, H.S. Lee, Lithospermic acid B isolated from Salvia miltiorrhiza ameliorates ischemia/reperfusion-induced renal injury in rats, *Life sciences*, 75(15) (2004) 1801-1816.
62. J.R. Liu, G.F. Chen, H.N. Shih, P.C. Kuo, Enhanced antioxidant bioactivity of Salvia miltiorrhiza (Danshen) products prepared using nanotechnology, *Phytomed.,*15(1-2) (2008) 23-30.
63. Q. Peng, T. Gong, J. Zuo, J. Liu, D. Zhao, Z. Zhang, Enhanced the oral bioavailability of salvianolic acid B by phospholipid complex loaded nanoparticles, *Die Pharmazie-An Inter. J. Pharm. Sci.*, 63(9) (2008) 661-666.
64. R.S. Lalchand, R. Gupta, R.O. Prakash, Cuscuta reflexa (dodder plant): a critical review on the medicinal plant used in ayurveda, *Inter. J. Res. Ayur. Pharm.*, 8(6) (2018) 38-42.
65. K. Umehara, K. Nemoto, T. Ohkubo, T. Miyase, M. Degawa, H. Noguchi, Isolation of a new 15-membered macrocyclic glycolipid lactone, Cuscutic Resinoside a from the seeds of Cuscuta chinensis: a stimulator of breast cancer cell proliferation, *Planta medica*, 70(04) (2004) 299-304.

66. L. Jian-Hui, J. Bo, B. Yong-Ming, A. Li-Jia, Effect of Cuscuta chinensis glycoside on the neuronal differentiation of rat pheochromocytoma PC12 cells, *Inter. J. Deve. Neuro.*, 21(5) (2003) 277-281.
67. X. Bao, Z. Wang, J. Fang, X. Li, Structural features of an immunostimulating and antioxidant acidic polysaccharide from the seeds of Cuscuta chinensis, *Pla. Med.*, 68(03) (2002) 237-243.
68. F.L. Yen, T.H. Wu, L.T. Lin, T.M. Cham, C.C. Lin, Nanoparticles formulation of Cuscuta chinensis prevents acetaminophen-induced hepatotoxicity in rats, *Food Chem. Toxicol.*, 46(5) (2008) 1771-1777.
69. M.Z. Abdin, K.J. Mirza, S. Khan, Development and detection efficiency of SCAR markers of Cuscuta reflexa and its adulterant Cuscuta chinensis, *J. Food Drug Ana.*, 20(2) (2012).
70. N. Nuengchamnong, A. Hermans-Lokkerbol, K. Ingkaninan, Separation and detection of the antioxidant flavonoids, rutin and quercetin, using HPLC coupled on-line with colorimetric detection of antioxidant activity, *Naresuan University Journal: Sci. Tech. (NUJST)*, 12(2) (2013) 25-37.
71. M.R. Schaab, B.M. Barney, W.A. Francisco, Kinetic and spectroscopic studies on the quercetin 2, 3-dioxygenase from Bacillus subtilis, *Biochem.*, 45(3) (2006) 1009-1016.
72. T. Pralhad, K. Rajendrakumar, Study of freeze-dried quercetin–cyclodextrin binary systems by DSC, FT-IR, X-ray diffraction and SEM analysis, *J. Pharma. Biomed. Ana.*, 34(2) (2004) 333-339.
73. E. Amanzadeh, A. Esmaeili, R.E.N. Abadi, N. Kazemipour, Z. Pahlevanneshan, S. Beheshti, Quercetin conjugated with superparamagnetic iron oxide nanoparticles improves learning and memory better than free quercetin via interacting with proteins involved in LTP, *Sci. Rep.*, 9(1) (2019) 1-19.
74. C.M. Spencer, D. Faulds, Paclitaxel, *Drugs*, 48(5) (1994) 794-847.
75. M. Breunig, S. Bauer, A. Göpferich, Polymers and nanoparticles: intelligent tools for intracellular targeting? *Euro. J. Pharma. Biopharm.*, 68(1) (2008) 112-128.
76. H.P.F.D. Fessi, F. Puisieux, J.P. Devissaguet, N. Ammoury, S. Benita, Nanocapsule formation by interfacial polymer deposition following solvent displacement, *Inter. J. Pharm.*, 55(1) (1989) R1-R4.
77. X. Dong, C.A. Mattingly, M. Tseng, M. Cho, V.R. Adams, R.J. Mumper, Development of new lipid-based paclitaxel nanoparticles using sequential simplex optimization, *Euro. J. Pharma. Biopharm.*, 72(1) (2009) 9-17.