Onyeji., Afr J Tradit Complement Altern Med., (20) 18 (1): 27 -35
https://doi.org/10.21010/Ajtcamv18i1.3

PROSPECTS OF INTEGRATION OF NANOTECHNOLOGY TO ANTIMALARIAL HERBAL REMEDIES FOR IMPROVED THERAPEUTIC EFFICACY – A CONCISE REVIEW

ONYEJI Cyprian .O.*

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria.

***Corresponding author Email:** cyprian.onyeji@unn.edu.ng

Article History
Received: Aug. 5th 2022
Revised Received: Aug. 24th 2022
Accepted: Dec. 8th 2022
Published Online: Dec. 22nd 2022

Abstract

Background: The therapeutic utility of herbal medicinal products including antimalarial herbal remedies has been hampered by some unfavorable biopharmaceutical properties of the bioactive constituents such as low aqueous solubility, poor oral bioavailability, poor intestinal permeability and large molecular size. Al these biopharmaceutical issues are responsible for observed reduced in vivo efficacy of some herbal products compared to their in vitro efficacy. These drawbacks can by countered by the integration of nanotechnology. The present article identified the various documented nanosystems and examined the recent efforts in the deployment of nanotechnology in formulations of antimalarial herbal medicines for improved therapeutic efficacies. Also safety considerations in clinical applications of nanoformulations were highlighted.
Methods: The information was acquired from an extensive literature searching of electronic databases such as Science-Direct, PubMed, and Google-Scholar to obtain appropriate articles made in the English language which were published up to 2022, using a combination of relevant keywords.
Results: Only very few herbal antimalarial remedies such as extracts of *Azadirachta indica***,** *Momordica charantia***,** *Curcuma longa*, and *Artemisia* species have been nanoformulated and evaluated for antimalarial efficacy. In all these studies, the drug-loaded nanoformulations exhibited significantly higher in vitro and/or in vivo antimalarial efficacy. The different nanoformulations of antimalarial herbal remedies that have been reported include lipid-based nanoparticles, cyclodextrin nanoparticles, chitosan/lecithin nanoparticles, solid lipid nanoparticles, conventional and polyethylene glycol liposomes, nanosuspension, nanoemulsions, and metal-based nanoparticles..
Conclusion: Different types of nanoformulations of herbal antimalarial drugs have been reportedly prepared by different techniques and these offer advantages of improved efficacies. Safety concerns present a hurdle to clinical applications.

Key words: Herbal medicine; Antimalarial; Nanoformulation; Nanotechnology

Introduction

Nanotechnology is the study, design, production and application of materials, structure and systems at the nanoscale dimensions which are approximately 1 to 100 nanometers. Nanoscale sized particles are known to have unique structural, physicochemical and biological properties, making nanotechnology to have a wide range of applications in Pharmaceutical sciences incorporating drug development, drug delivery systems, and diagnosis. Other applications are in agriculture, medicine, electronics, energy, etc. In nanoscale medicines, the drugs are encapsulated or attached to nanostructures which confer several benefits, as depicted in Fig. 1, which include (i) Improvement of oral bioavailability of the drug resulting from increased aqueous solubility due to their nanoscale size and large surface area, (ii) protection of drugs from destruction in the gastrointestinal region, (iii) delivering the drug at a controlled rate or to targeted locations, and (iv) facilitating improved uptake of the drug by various cells types (Mazayen *et al*, 2022).

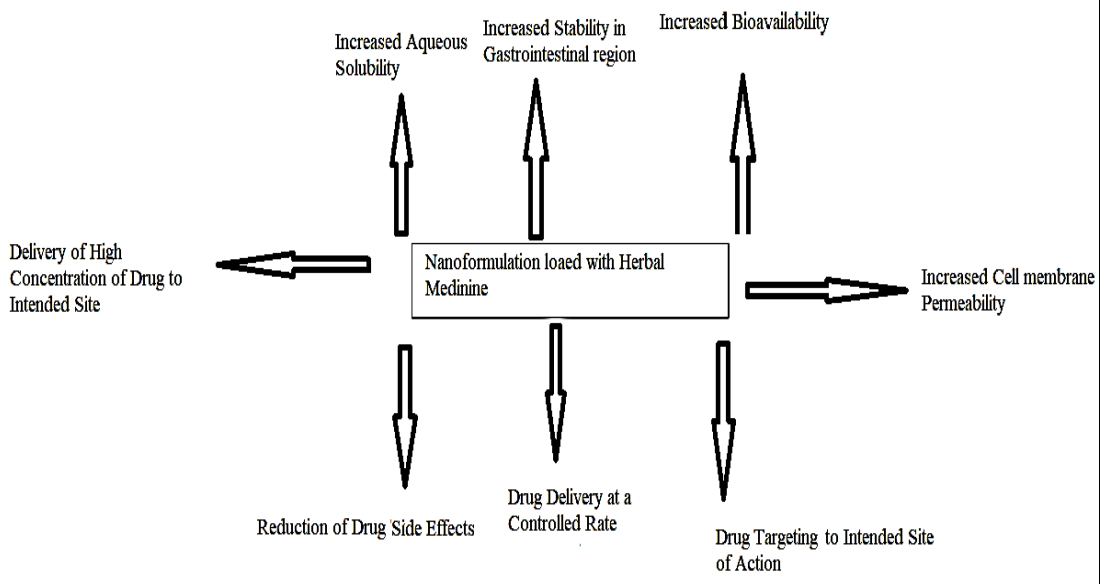


Fig.1: Diagram Depicting advantages derivable from Nanoformulation of Herbal Medicinal Products

Several studies have been geared towards identifying and validating efficacies of Herbal Medicinal Products (HMPs) and other natural compounds in the treatment of several major diseases including malaria. Malaria, an infectious disease caused by plasmodium parasites, continues to constitute a major public health concern as it remains a leading cause of morbidity and mortality in many developing countries. According to the WHO malaria report of 2021, malaria cases increased from 227 million in 2019 to an estimated 241 million malaria cases in 2020, with most of this increase reported from countries in the WHO African Region which accounted for 95% of the malaria cases (WHO 2021). The increasing resistance of malaria parasites to conventional antimalarial drugs re-enforced the need for exploration of new antimalarial agents. Antimalarial herbal products have served as highly promising sources of new antimalarial agents. Indeed, herbal medicines have been in use for treatment of malaria for centuries, and high prevalence in use of various HMPs has been reported in developing and developed countries (Hunt *et al*, 2010; Ekor 2014). The attraction in HMPs and natural drugs is attributed to several factors including the verified or unverified claims of their effectiveness along with the perception that, being natural in origin, the remedies are safer, less in toxicity and cost-effective. Also, the use of HMPs is associated with the conviction that in situations where orthodox drugs have proven to be ineffective, herbal medicines might be a good alternative (Ekor, 2014). In spite of the good therapeutic potentials ascribed to the use of HMPs, a good number of them fail when subjected to clinical trials and this is due to their unfavorable physicochemical properties such as low aqueous solubility, high molecular size, poor bioavailability and inability to cross lipid membranes. There are abundant cases of herbal products with outstanding in vitro activities but with very poor in vivo efficacy due to the physicochemical limitations of the bioactive constituents (Oladimeji *et al*, 2018). To overcome these challenges, a range of nanotechnology-based systems have been developed for commercially available orthodox drugs, also, a number of reviews have reported studies on herbal medicines formulated with drug delivery systems based on nanotechnology (Patra *et al*, 2018; Moradi *et al*, 2020; Sandhiya & Ubaidulla, 2020)

The literature abounds with studies on a wide variety of plants belonging to several families that have been identified as antimalarial medicinal plants and it was documented that malaria treatment had been done with 1277 plant species from 160 families from different parts of the world (Bahekar S, Kale R 2013; Wilcox *et al*, 2011). However, only a few of these single-herb remedies, when taken through clinical trials, have demonstrated efficacy (Onyeji *et al*, 2017). The unfavorable physicochemical properties of these bioactive phytoconstituents could have resulted in their diminished bioavailability and/or poor intestinal permeability. A typical example is the extract of *Azadirachta indica* which exhibits high in vitro activity against various *Plasmodium falciparum* strains but poor in vivo activity (Adebayo & Krettli, 2011). The present review identified the various nanosystems and examined the recent efforts in the application of nanotechnology in formulations of antimalarial herbal medicines for improved therapeutic efficacies. Also safety concerns in clinical applications of nanoformulations were highlighted.

Methodology

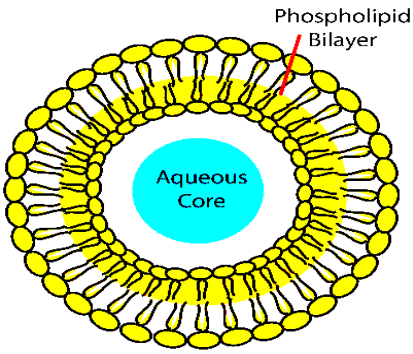
A literature search was extensively undertaken so as to obtain appropriate research publications made in the English language. Different electronic databases such as Google Scholar, PubMed, and Science Direct were used to search for articles published up to 2022 with combinations of the following keywords: “nanotechnology”, “nanoformulation”, “herbal”, “herbal antimalarials”, “nanocarrier types”, and “nanoformulations safety”.

Nanotechnology-based formulations and Techniques used in the formulation

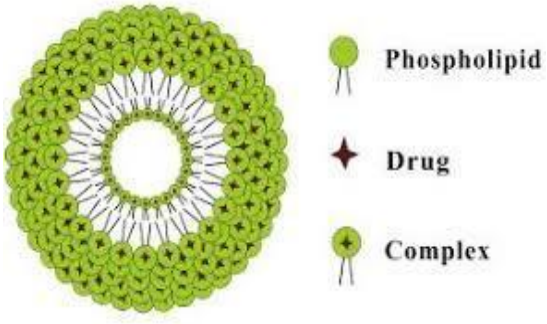
The literature is replete with reviews on nanosystems, materials and techniques used in their formulations (Patra *et al*, 2018; Onyeji 2018; Sandhiya & Ubaidulla, 2020]. Table 1 shows examples of the nanosystems used for drug delivery with their compositions while schematic representations of their structures are depicted in Fig.2. The major types of nanoformulations include liposomes, Lipid nanoparticles, Phytosomes, Nanoemulsions, Transferosomes, Ethosomes, Niosomes,
β-cyclodextrin complexes, Dendrimers, Mesoporous Silica Nanoparticles, Polymeric nanomicelles, and polymeric nanoparticles.

Table 1: Nanosystems, their compositions and other characteristics (Patra *et al*, 2018; Onyeji 2018; Sandhiya & Ubaidulla, 2020].

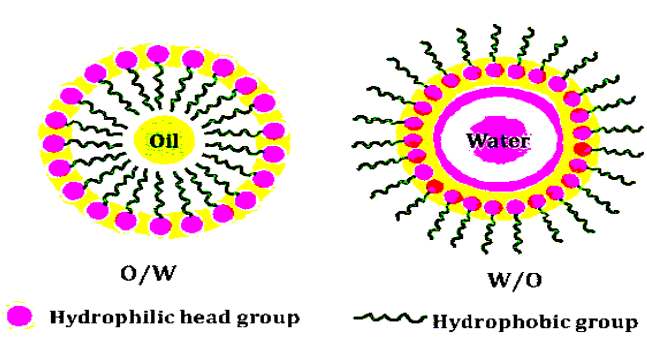
Nanosystem	Composition and other Characteristics
Liposomes	These are spherical vesicles consisting of one or more phospholipid bilayers that encapsulate polar and nonpolar materials. Liposomes have been shown to enhance solubility, bioavailability and intracellular uptake of the entrapped materials (Drug or HMP)
Lipid nanoparticles	There are three different types depending on type of lipid and preparation technique. These are Nanostructured lipid carriers, lipid drug conjugates and Solid Lipid Nanoparticles (SLN). The lipids used are biodegradable and are generally recognized as safe. This nanostructure is efficient as carriers for poorly water-soluble agents and improves drug transport across biological membranes.
Phytosomes	These are Phospholipids which form complexes with the medicine leading to enhanced absorption of the complexed material and improvement of bioavailability. Unlike in liposomes, there is no drug encapsulation.
Nanoemulsions	They are oil-in-water (o/w) emulsions with droplet size in the nanoscale range. They provide advantage of solubilization of hydrophobic molecules in the oily phase,
Transferosomes	These are similar to liposomes but their structure is deformable as a result of the incorporation of surfactants in the lipid bilayer. So, they are liposomes with flexible structure.
Ethosomes	This is another variety of liposome with a flexible structure due to incorporation of alcohol into the lipid bilayer. This has advantage of being able to carry materials with a wider range of polarities.
Niosomes	This is also a variety of liposomes with a flexible structure due to incorporation of non-ionic surfactants into the lipid bilayer. It has a greater chemical stability than liposomes and can carry medicines with a wider range of polarities.
β-cyclodextrin complexes	Cyclodextrins are a family of cyclic oligosaccharides consisting of 5 or more α-D-glucopyranoside units. They are non-toxic compounds that form soluble complexes having a cavity that can encapsulate materials with molecular weights between 200 and 800 g/mol, resulting in improvement of drug solubility and bioavailability
Dendrimers	These are nano-sized highly-branched polymeric structures that can often adopt a spherical morphology with a central core that encapsulates materials. The large number of peripheral groups can be functionalized for targeted drug delivery.
Mesoporous Silica Nanoparticles	These are nanosized, porous and honeycomb-like structure of silica (SiO_2). The porous structure, biocompatibility, nanoscale size, and larger surface area of this material offers advantages for drug entrapment and delivery. These have emerged as a promising innovative drug delivery system due to these favorable properties which also include high drug loading and controlled release kinetics.
Polymeric nanomicelles	These are a group of amphiphilic surfactant molecules that aggregate rapidly in water forming a nano-sized spherical vesicle. The center of the micelle is hydrophobic which enables entrapment of lipophilic medicines
Polymeric nanoparticles	They are colloidal drug delivery carriers with particle size of 10 to 100 nm and are prepared by employing biodegradable, synthetic, and natural polymers. Examples of various biodegradable polymers used in the fabrication of polymeric nanoparticles include poly(lactide) (PLA), poly (ε-caprolactone) (PCL), poly(lactide-co-glycolide) (PLGA) copolymers and also some natural polymers such as alginate, chitosan, lecithin, gelatin, and albumin. The efficiency of oral drug delivery is significantly affected by polymer molecular weight, method of preparation, particle size, and type of stabilizer



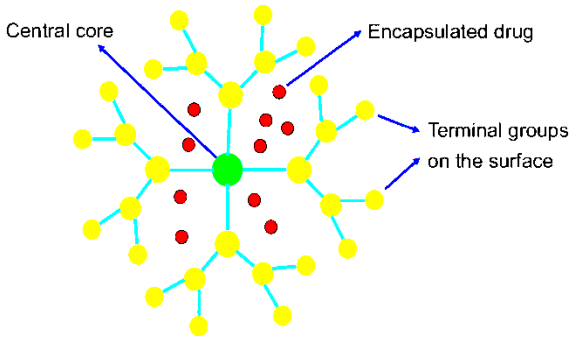
Liposome



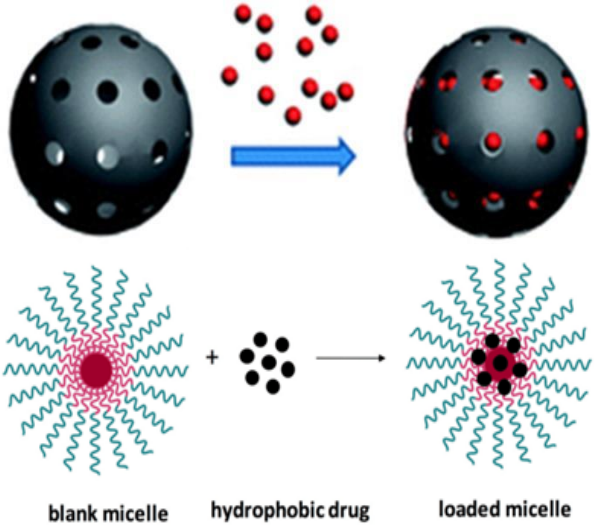
Phytosome



Nanoemulsion

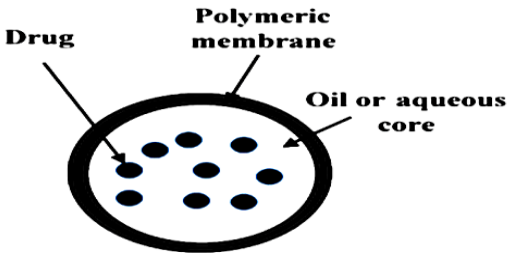


Dendrimer

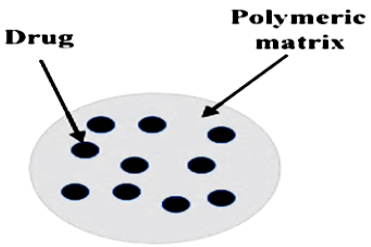


Polymeric Nanomicelle

Mesoporous Silica Nanoparticle



Nanocapsule



Nanosphere

Polymeric Nanoparticle

Figure 2: Schematic Representation of Structures of Different Nanosystem Particles

Nano-formulations Incorporating Antimalarial Herbal Medicines

Many phytoconstituents with good in vitro activity have poor aqueous solubility, large molecular size, and limited ability to cross the lipid–cell membranes, resulting in low bioavailability and loss of effectiveness. Preparation of these phytoconstituents as nanoformulations can significantly overcome these challenges resulting in increased efficacy and reduction of the side effects of various herbal medicines. Thus, this is the main essence of applying nanotechnology approach to drug delivery in HMPs. In addition, nanosystems can be used for targeted drug delivery such that the herbal medicine is delivered to specific tissues/organs which improve the selectivity, efficacy and decreased side effects. More advantages include the possibility of use of the nanoparticles with high loading capacities to deliver high concentrations of drugs to required site of action, and this further enhances treatment efficacy. In the treatment of malaria, it is an attractive approach for the development of customized nanosystems capable of delivering antimalarial medicines targeted at *Plasmodium* in hepatic and erythrocytic stages. An extensive literature search revealed that numerous HMPs used for varied disease conditions have been formulated with different types of nanosystems with the objective of improving the efficacies and reducing the side effects of the herbal medicines. A review by Mathur (2016) gave a compilation of up to 150 herbal drugs with diverse biological activities that have been formulated with different nanotechnology tools. However, only limited studies have been reported on nanoformulations of herbal antimalarial medicines.

Nanoformulation of leaf extracts of *Azadirachta indica* (neem)

The plant, *Azadirachta indica (neem)* is commonly available and has been found to demonstrate in vitro antiplasmodial and in vivo antimalarial efficacies, amongst other biological activities. Sardana *et al* (2018) formulated silver nanoparticles incorporating a combination of *Azadirachta indica* and *Ocimum sanctum* plant leaf extracts, and evaluated the antiplasmodial activity of the nanoparticle. The antiplasmodial activity was studied using the *Plasmodium falciparum*, 3D7, malarial parasite strain in RPMI 1640 medium, and nonlinear regression analysis was used to calculate the half maximal effective concentration values (EC_{50}). The results showed that silver nanoparticles formulation of the aqueous leaf extracts of combination of the two plants resulted in significant improvement on the antiplasmodial activity of the plant extracts (Sardana *et al*, 2018). In a more recent study, aqueous leaf extracts of *Azadirachta indica* alone was formulated as silver nitrate nanoparticles and the anti-plasmodial activity was tested using two lab-adapted *Plasmodium falciparum* strains, 3D7 (chloroquine-sensitive), and W2 (chloroquine-resistant). The results indicated that, the half inhibitory concentration (IC_{50}) of the nanoformulation had a four-fold decrease against both parasite strains when compared to aqueous neem leaves extract (Ghazali *et al*, 2022).

Nanoformulation of *Momordica charantia* leaf extract

Momordica charantia also known also as bitter melon generally grows in tropical regions. The plant has been reported to have a wide range of bioactivities and phytochemical studies revealed that the leaf extracts contain alkaloids, saponins, glycosides, phenolic constituents, reducing sugars and free acids (Ghandi *et al*, 2018). TiO_2 nanoparticles were synthesized using the *Momordica charantia leaf* aqueous extract. The antimalarial activity of the leaf aqueous extract and synthesized TiO2 nanoparticles were evaluated against CQ-resistant and CQ sensitive strains of *Plasmodium falciparum*. The results showed that incorporation of the aqueous extract in TiO2 nanoparticle resulted in significant decreases in the IC_{50} values for both strains compared to the values for M. charantia leaf aqueous extract alone. (Ghandi *et al*, 2018).

Nanoformulation of curcumin

Curcumin is the main natural polyphenol found in the rhizome of *Curcuma longa* (also called turmeric) and in others *Curcuma* spp. *Curcuma longa* has been used as a medical herb due to its numerous biological activities, and has also been shown to have antimalarial activity (Reddy *et al* 2005). However, the clinical use of this herbal extract is limited by its poor oral absorption due to its very low aqueous solubility and extensive intestinal metabolism. These drawbacks are being circumvented by using different strategies including encapsulation in different nanosystems (Akhtar et a, 2012). Over the years, a number of reports have shown studies on diverse nanoformulations of curcumin using different materials and techniques. All the studies were aimed at improving the oral bioavailability of curcumin with the purpose of enhancing its antimalarial efficacy.

A study investigated curcumin –loaded hydrogel nanoparticles with the objective of exploiting the size and hydrophilic nature of the formulated nanosystem so as to improve the bioavailability and also reduce the rate of systemic clearance of curcumin. Using mice malaria infection model, the drug-loaded nanoparticles had superior in vivo anti-malarial activity compared to curcumin control, while toxicity studies established the safety of the formulation following oral administration (Dandekar *et al*, 2010). In another study, curcuminoids-loaded lipid nanoparticles prepared by a nanoemulsion technique was invested for in vivo antimalarial efficacy. The results revealed a 2-fold increase in antimalarial activity of loaded lipid nanoparticles in comparison to free curcuminoids, at the same dosage levels (Nayak *et al*, 2010). Furthermore, a study has shown that oral delivery of chitosan nanoparticles loaded

with curcumin improved the bioavailability of curcumin and also increased its uptake by red blood cells (Akhtar *et al*, 2012). In evaluating the antimalarial efficacy of the curcumin-loaded chitosan, it was found that the survival duration of mice infected with a lethal strain of Plasmodium yoelii (N-67) was significantly longer with administration of the nanoformulation compared to the effect of administration of curcumin alone. For example feeding 1 mg of curcumin to infected mice per day for seven days resulted in 33 % survival while administration of 1 mg of curcumin bound to chitosan nanoparticles resulted in 100% survival (Akhtar *et al*. 2012). Many more authors have prepared different nanoformulations of curcumin. Ghosh *et al* (2014) prepared and characterized nanotized curcumin by a modified emulsion-diffusion-evaporation method, and investigated its antimalarial efficacy both in vitro and in vivo. The curcumin-loaded nanoparticle was found to be ten-fold more effective for in vitro growth inhibition of *Plasmodium falciparum* relative to the drug alone. The nanotized curcumin was also found to have a much higher oral bioavailability compared to the free curcumin. In addition, treating *Plasmodium berghei*-infected mice with nanotized curcumin administered orally resulted in a significant prolongation of their survival in comparison with the free curcumin-treated infected mice. Alam *et al* (2016) formulated biocompatible short peptide-based nanoparticles and investigated their potential as drug delivery systems for curcumin and also determined whether the nanoformulation can improve the antimalarial activity of curcumin. Both in vitro and in vivo studies showed enhanced antimalarial activity with curcumin-entrapped dipeptide nanoparticles compared to the free drug. The in vivo antiplasmodial activity and the toxicity assessment of curcumin incorporated into poly (lactic-co-glycolic) acid (PLGA) nanoparticles were studied by Busari *et al* (2017). The percentage parasite suppression with drug-loaded nanosystem was significantly higher compared to the free drug of the same dose. Also, the toxicity assessment parameters showed no significant differences at low drug doses between the free and PLGA encapsulated form. In yet another study, curcumin was loaded in nanostructured lipid carriers and evaluated for malaria treatment. The results of in vivo antiplasmodial activity using *P. berghei* model demonstrated that the antimalarial activity of the nanosystem containing curcumin was significantly higher compared with that of free curcumin at the same dose (Rashidzadeh *et al*, 2019). In another study in the same year, orally-administered curcumin-loaded liposomes modified to contain eudragit (a pH-sensitive co-polymer) and nutriose (a carbohydrate polymer of vegetable origin) resulted in highly significant increase in the survival of malaria-infected mice compared to free curcumin-treated controls. The stability of the liposomes in the GIT fluid was enhanced by the liposomal contents of eudragit, known to be gastro-resistant, and nutriose which is known to be enzyme-digestion-resistant (Manconi *et al*, 2019).

All these studies have shown that nanoformulations of curcumin prepared with diverse carriers and different techniques, are potential delivery nanosystems for the treatment of malaria.

Nanoformulation of Artemisia species extract

The genus *Artemisia* has more than 500 species, some of which have been used as remedies for different conditions including malaria. The therapeutic action is attributable to the presence of a large variety of terpenes and thujones found in their extracts. *Artemisia annua* is the main source of the antimalarial compound, artemisinin, but other species such as *A.absinthium*, *A. afra*, *A. herba-alba*, and *A. sieberi* have also been widely used as antimalarial remedies. The bio-efficacy of Artemisia extracts as well as artemisinin is limited by their unfavorable characteristics including low aqueous solubility, poor oral bioavailability and short elimination half-life. These shortcomings have been counteracted by employing nanotechnology-based drug delivery systems that have been prepared with different nanoparticles (Avitabile *et al*, 2020). For example, two *Artemisia* species (*A. abrotanum* and *A. arborescens*) have been used to prepare and characterize silver nanoparticles and their potential antimalarial efficacy were evaluated in vitro using *Plasmodium falciparum* cultures. The results showed that the IC_{50} values were significantly lower with the two extract-silver nanoparticles relative to the free extracts or silver nanoparticle without the extract (Avitabile *et al*, 2020). The major antimalarial bioactive compound in artemisia sp is artemisinin. To enhance the low aqueous solubility and poor bioavailability of artemisinin, various researchers have produced different types of nanoformulations of the compound and evaluated their antimalarial efficacies. These various nanoformulations loaded with artemisinin include PLGA-based nanoparticles, self-assembled biotransesterified cyclodextrin nanoparticles, chitosan/lecithin nanoparticles complexed with β-cyclodextrin, solid lipid nanoparticles, conventional and polyethylene glycol (PEGylated) liposomes, nanosuspension, nanoemulsions, and metal-based nanoparticles. In all these studies, the artemisinin-loaded nanoformulations exhibited significantly higher in vitro and/or in vivo antimalarial efficacy [Alven *et al*, 2020]

Safety Considerations

Due to the unique biopharmaceutical properties of herbal-nanomedicines, it is evident that they possess the potential to have a positive impact in therapeutics. The development and introduction into clinical use of any product, including herbal nanoformulations, requires following ethical and safety standards as specified in national and international regulations and guidelines. It is recognized that toxicity in the biological system is a major concern and limitation associated with delivery of herbal medicines through nanoformulation. This is despite the fact that studies have shown that many herbal-nanoparticles are biodegradable in nature, but, studies have also shown that some of the nanoparticles have side effects even when they are made of biocompatible and biodegradable materials. It is imperative that the toxicity of not only the herbal product itself is examined, that of the applied nanomaterial should

also be investigated. For example, lipid and polymeric nanoparticles with positively charged surface have shown that, unlike neutral charged nanoparticles, they could cause apoptosis and release of mediators with higher toxic effect, and this is due to their increased interaction with cell membranes (Beg *et al*, 2020). Another example is that some metal nanoparticles primed with lipopolysaccharide caused oxidative DNA damage, disruption of the cell membrane, and programmed cell death (Beg *et al*, 2020). Apart from the intrinsic toxicity of the nanomaterials, it is known that, since nanosized particles can cross cell membranes and break biological barriers, nanoparticles can alter the pharmacokinetics of the entrapped medicines resulting in alteration of the therapeutic effect along with toxicity profiles. Thus, the drug-loaded nanoparticles can reach tissues and sites of bioactivity which the free drug cannot normally get to. This has implication for manifestation of a different toxicity profile compared to the free drug or nanomaterial. Also, the nature/type of drug delivery carrier can cause significant differences in the pharmacokinetics of the drug loaded in nanoformulations, hence, each type of nanoformulation requires separate efficacy and safety evaluations. Furthermore, the bioavailability enhancement of herbal medicines through nanoformulations comes with additional responsibility of determination of appropriate dosage regimen of the nanoformulation so as to ensure safety. Therefore, cognizance should be accorded to the safety issues related to herbal nanoformulations and they should be subjected to standard scientific tests. It is noteworthy that a number of herbal medicines in nanoformulations have gone through clinical trials and are currently available in the market, Examples include Green tea liposome Herbasec®, (a *Camellia sinensis* extract), Silymarin Phytosome® (Silymarin from Milk Thistle seed), Guarana liposome Herbasec® (Guarana extract), Leucoselect® or Phytosome® (Polyphenol from grape seed) etc (Beg *et al*, 2020).

Conclusion and Future Prospects

The therapeutic utility of the herbal medicinal products has been acknowledged since long ago, but efforts are now being made to enhance their therapeutic efficacies by overcoming their unfavorable biopharmaceutical characteristics. The development of novel drug delivery systems such as nanoformulation has presented opportunities for circumventing these drawbacks. The effectiveness of drug delivery through nanoformulation is principally based on efficient entrapment of the drugs by the nanoparticles, and the effective delivery of drug to the targeted site within the body, followed by a successful release of the drug. Herbal medicines have been in use for treatment of malaria for centuries, but there are several reports of the herbal products showing good activity in vitro but with poor in vivo efficacy. This is attributable to the unfavorable physicochemical properties of the bioactive phytoconstituents which can be overcome through delivery as nanoparticles. Very limited studies have been reported on nanoformulations of herbal antimalarial medicines. This shows that herbal antimalarial nanoformulation and evaluations of their efficacy and safety provide a very wide research area that needs exploration. For instance, Lemma *et al* (2017) documented 752 medicinal plants traditionally used for malaria treatment and investigated their in vitro antiplasmodial efficacies. Among the plants identified as having good antiplasmodial crude extracts are *Harungana madagascariensis*, *Quassia africana,* and *Brucea javanica*, while *Picrolemma spruce*, *Aspidosperma vargasi*, *Aspidosperma desmanthum,* and *Artemisia Annua* were reported to have very good antiplasmodial activities. Out of these herbs only extract of *Artemisia annua* has so far been nano-formulated and the in vivo antimalarial efficacy was remarkably improved compared to the free extract.

Evident from the extensive literature search undertaken for this article, over the past decades, huge efforts were made and significant achievements have been recorded by researchers in the field of nanotechnology but, clinical application is still limited for herbal nanoparticles, This is because of several impediments such as the issues of stability and reproducibility of nanoparticles, low entrapment efficiency of herbal medicines by nanoparticles, and notably, the high production cost. Also, unlike orthodox medicines which are based on a single chemical entity for a single target, the herbal medicinal products contain multiple bioactive chemical compounds and this presents another challenge in terms of accurate determination of release profile of bioactive compounds in nanomedicines, to enable prediction of in vivo delivery (Beg *et al*, 2020). However, the applications of nanotechnology in the formulation of herbal medicinal products have opened new avenues for improving the safety and efficacy of herbal products for treating different diseases (Marthur, 2016; Zhang *et al*, 2021). It is anticipated that in the not-too-distant future, research endeavours would be geared towards the development and deployment of surface-modified nanosystems for improved drug targeting to intended tissues.

References

1. Adebayo, J.O. and Krettli, A.U. (2011). Potential antimalarials from Nigerian plants: A review. J Ethnopharmacol. 133:289–302.
2. Akhtar, F., M., Rizvi, M.M.A., and Kar, S.K.. (2012). Oral delivery of curcumin bound to chitosan nanoparticles cured Plasmodium yoelii infected mice, Biotechnology Advances 30: 310–320.
3. Alam, S, Panda, J.J., Mukherjee, K.T. and Virander Singh Chauhan V.S. (2016). Short peptide based nanotubes capable of effective curcumin delivery for treating drug resistant malaria. J. Nanobiotechnol 14:26. DOI 10.1186/s12951-016-0179-8.
4. Alven, S., and Aderibigbe, B.A. (2020). Nanoparticles Formulations of Artemisinin and Derivatives as Potential Therapeutics for the Treatment of Cancer, Leishmaniasis and Malaria. Pharmaceutics 12: 748; doi:10.3390 /pharmaceutics12080748.
5. Avitabile, E, Senes, N, D'Avino, C., Tsamesidis, I., Pinn, A., and Medici S. (2020). The potential antimalarial efficacy of hemocompatible silver nanoparticles from Artemisia species against P. falciparum parasite. PLoS ONE 15(9): e0238532. https://doi.org/10.1371/journal.
6. Bahekar, S. and Kale R (2013). Herbal Plants Used for the Treatment of Malaria- A Literature Review. J. Pharmacogn. Phytochem. 1(6):141-146.
7. Beg, S., Barkat, M.A., and Ahmad F.J. (Editors). Nanophytomedicine: Concept to Clinic. Springer Nature Singapore Pte Ltd. 2020.
8. Busari, Z.A., Dauda , K.A., Olajumoke A Morenikeji, O.A., Afolayan , F., Oyeyemi, O.T, Meena, J , Sahu, D. , and Panda, A.K .(2017). Antiplasmodial Activity and Toxicological Assessment of Curcumin PLGA-Encapsulated Nanoparticles. Front Pharmacol. 6;8:622. doi: 10.3389/fphar.2017.00622.
9. Dandekar, P.P., Jain, R., Patil, S., Dhumal, R., Tiwari, Sharma, S., Vanage, G., and Patravale, V. (2010), Curcumin-Loaded Hydrogel Nanoparticles: Application in Anti-Malarial Therapy and Toxicological Evaluation. J Pharm Sciences 99(12): 4992-5010.
10. Ekor, M (2014). The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front. Pharmacol. 4(177):1-9.
11. Gandhi, P.R, Jayaseelan, C., Kamaraj, C., Rajasree, S.R.R., and Mary R.R. (2018). In vitro antimalarial activity of synthesized TiO2 nanoparticles using Momordica charantia leaf extract against Plasmodium falciparum. J. Appl. Biomed. 16 (4): 378-386. https://doi.org/10.1016/j.jab.2018.04.001.
12. Ghazali, S.Z., Noor, N.R.M. , and Mustaffa, KMF. (2022). Anti-plasmodial activity of aqueous neem leaf extract mediated green synthesis-based silver nitrate nanoparticles. Prep Biochem Biotechnol 52(1): 99-107. doi: 10.1080/10826068.2021.1913602.
13. Ghosh, A., Banerjee, T., Bhandary, S., Surolia, A. (2014).. Formulation of nanotized curcumin and demonstration of its antimalarial efficacy. Int J Nanomed 9: 5373–5387.
14. Hunt, K.J., Coelho, H.F., Wider, B, Perry, R., Hung, S.K, Terry, R, and Ernst E (2010). Complementary and alternative medicine use in England: results from a national survey. Int. J. Clin. Pract. 64(11):1496-1502.
15. Lemma, M.T., Ahmed, A.H., Elhady, M.T. Ngo, H.T., Le-Huy Vu, T., Sang, T.K., Campos-Alberto, E., Sayed, A., Mizukami, S., Na-Bangchang, K., Huy, N.T., and Hirayama, K. (2017) Medicinal plants for in vitro antiplasmodial activities: A systematic review of literature. Parasitol Int. 66(6): 713-720. doi: 10.1016/j.parint.2017.09.002.
16. Manconi, M., Manca, M.L., Escribano-Ferrer, E., Coma-Cros, E.M., Biosca, A.,Lantero, E., Fernàndez-Busquets, X., Fadda, A.M., and Caddeo, C.. (2019). Nanoformulation of curcumin-loaded eudragit-nutriosomes to counteract malaria infection by a dual strategy: Improving antioxidant intestinal activity and systemic efficacy. Int J Pharm. 556: 82-88
17. Mathur, M (2016). Achievements, constraints and gaps of nanotechniques pertains to augmenting herbal drug efficacy. Medicinal Plants. 8 (3): 171-198.
18. Mazayen, Z.M, Ghoneim A.M, Elbatanony, R.S., Basalious, E.B. and Bendas, E.R. (2022). Pharmaceutical nanotechnology: from the bench to the market. Future J of Pharm. Sci. 8:12 https://doi.org/10.1186/s43094-022-00400-0.
19. Moradi, S.Z, Momtaz, S, Bayrami, Z, Farzaei M.H and Abdollahi M. (2020). Nanoformulations of Herbal Extracts in Treatment of Neurodegenerative Disorders. Front. Bioeng. Biotechnol. 8:238. doi: 10.3389/fbioe.2020.00238.
20. Nayak, A.P., Tiyaboonchai, W., Patankar, S., Madhusudhan, B Eliana B.Souto, E.B. (2010). Curcuminoids-loaded lipid nanoparticles: Novel approach towards malaria treatment. Colloids and Surfaces B: Biointerfaces. 81(1): 263-273.
21. Oladimeji, F.A., Adegbola, A.J., and Onyeji, C.O. (2018). Appraisal of Bioenhancers in Improving Oral Bioavailability: Applications to Herbal Medicinal Products. J. Pharm. Research Int. 24(4): 1-23.
22. Onyeji, C.O., Igbinoba, S.I., Olayiwola G. Adehin, A. (2017). Insight into clinically effective herbal antimalarial products: Effects on drug metabolizing enzymes and p-glycoprotein. Af J harm Pharmacol. 12(48): 591-613.

23. Onyeji CO. (2018). Nanoparticles: Key to Optimization of Drug Therapy. Adv Pharmacol Clin Trials 3(1): 000125.
24. Patra, J.K. , Das, G., Fraceto, L.F., Campos, V.R., Rodriguez-Torres, M.D., Acosta-Torres, L.S., Diaz-Torres, L.A. , Grillo, R., Swamy, M.K., Sharma, S, Habtemariam, S. and Shin, S. (2018). Nano based drug delivery systems: Recent developments and future prospects. J Nanobiotechnol 16:71 https://doi.org/10.1186/s12951-018-0392-8.
25. Rashidzadeh, H., Salimi, M., Sadighian, S., Rostamizadeh, K.; Ramazani, A. (2019). *In vivo* Antiplasmodial Activity of Curcumin-Loaded Nanostructured Lipid Carriers. Current Drug Delivery, 16(10): 923-930. DOI**:** https://doi.org/10.2174/1567201816666191029121036.
26. Reddy, R.C., Vatsala, P.G., Keshamouni, V.G., Padmanaban, G., Rangarajan, P.N. (2005).. Curcumin for malaria therapy. BBRC 326(2):472–474.
27. Sandhiya, V. and Ubaidulla, U. (2020). A review on herbal drug loaded into pharmaceutical carrier techniques and its evaluation process. Future J of Pharm. Sci. 6:51 https://doi.org/10.1186/s43094-020-00050-0
28. Sardana, M., Agarwal V., Pant A., Kapoor V., Pandey K.C, Kumar, S. (2018). Antiplasmodial activity of silver nanoparticles: A novel green synthesis approach. Asian Pacific Journal of Tropical Biomed. 8(5): 268-272.
29. Willcox, M, Benoit-Vical, F, Fowler, D, Bourdy, G, Burford, G, Giani, S, Graziose, R, Houghton, P., Randrianarivelojosia, M, and Rasoanaivo, P. (2011). Do ethnobotanical and laboratory data predict clinical safety and efficacy of anti-malarial plants? Malar. J. 10 (Suppl 1):S7.
30. World malaria report 2021. Geneva: World Health Organization; 2021.
31. Zhang, J., Hub, K., Di, L., Wang, P., Liu, Z., Zhang, J., Yue, P. , Song, W, Zhang, J., Chen, T., Wang, Z., Zhang, Y, Wang, X, Zhanm, C., , Cheng Y.C, Li, X, Li, Q., Fan, J.Y, Shen, Y., Han, J.Y., and Qiao, H. (2021). Traditional herbal medicine and nanomedicine: Converging disciplines to improve therapeutic efficacy and human health. Advanced Drug Delivery Reviews 178: 113964.