J. Mat. NanoSci. 2018, 5(1), 35-60 Review

Journal of
Materials NanoScience

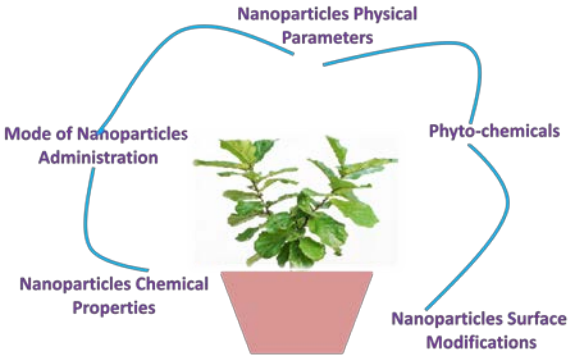
Herbal nanomedicine interactions to enhance pharmacokinetics, pharmacodynamics, and therapeutic index for better bioavailability and biocompatibility of herbal formulations

Rajiv Kumar[1*], Munesh Sharma[2]

[1]*University of Delhi, Delhi. India.* [2]*Ayurvedic Clinic Arogya Nidhi, and Ayurveda Clinic, Rohini, Delhi. India.*

Submitted on: 21-Mar-2018, Accepted and Published on: 11-May-2018

ABSTRACT



The recent developments in nanotechnology have unlocked new avenues in current research and play a key role in upgrading the therapeutic index of phytomedicine and herbal remedies. The systematically developed nanoparticles are highly capable of enhancing the possibilities of the development of novel herbal-nanomedicine (HNM). The nanoformulations can overcome the problems that persisted in the old-style herbal remedies. The rigors survey of the reported literature evidenced that researchers have analyzed the interactions between nanomaterials and herbal remedies extensively to understand HNM interface and herbal interaction, and to find out various features of the enriched phytochemicals and herbal remedies such as bioavailability, biocompatibility, pharmacokinetics, pharmacodynamics, and therapeutic index. The full-fledged formulation has all the active ingredients required for an emerging HNM formulation in the form of nano dosage. These formulated doses have a higher therapeutic index compared to the earlier phytochemicals and herbal remedies. The assessment converses nanoscale herbal-nanomedicine as a potential therapeutic option and the drug delivery carrier. By employing ultramodern techniques and using the current knowledge required for the advancement of HNM, it is possible to enhance the therapeutic index of the herbal remedies. Finally, the novel HNM formulation can be a reality. To overcome the associated problems that existed in the improvement's route, the clinical pharmacokinetics and pharmacodynamics, several efforts have been done in the past. The interrelated findings have been included in the discussion. The therapeutic profile of HNM have been underlined including various pharmacokinetic and pharmacodynamic parameters i.e. absorption, distribution, metabolism, and excretion. These facts were listed as per the principles and entitlement of the therapeutic index. These parameters are important and necessarily required for the innovation of the non-toxic and novel herbal-nanomedicine.

Keywords: Phytomedicine, Herbal nanoparticle interactions, Hydrophilicity, Lipophilicity, Bioavailability, Nanocarriers

INTRODUCTION

Nanotechnology is one of the fastest-growing areas in the development and innovation of novel medicines. It is the most effective and far-reaching innovative technology in the existing scientific world. There are extreme demands for the scientific interpretation to predict and forecast the impact of multifunctional nanomaterials and nanoparticles in the formulation of herbal-nanomedicine and phytomedicine. The multifunctional nanoparticles are included in different proportions to achieve high biocompatibility, good biodegradability, low toxicity, excellent immunogenicity, tunable hydrophobic, and hydrophilic properties are these are considered as suitable source for the formulation of applicable herbal-nanomedicine. Using nanotechnology in the improvement of phytotherapy, up-gradation, and alteration of the

*Corresponding Author: Dr. Rajiv Kumar
Tel: +91-9810742944
Email: chemistry_rajiv@hotmail.com

Cite as: *J. Mat. NanoSci., 2018, 5(1), 35-60.*
urn:nbn:sciencein.jmns.2018v5.90

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herbal remedies is an essential perspective to prepare the novel herbal nanomedicine. Upgraded herbal-nanomedicines can treat various fatal diseases. The emerging nanotechnologies have enabled towards improved novel kinds of therapeutics. The nanomaterials and nanoparticles expressively enhance the pharmacokinetics, pharmacodynamic, and therapeutic index of herbal medications and phytomedicine. Nanoparticles comprise competent materials, such as biodegradable polymers, inorganic materials, lipids, organic materials, and polysaccharides. For a specific outcome and improved quality, the native form of the herbal remedies incorporate in the nanoparticles to get desirable herbal-nanomedicine formulation. Certain novel herbal-nanomedicines (HNM) have location-specific action and encoded well-ordered rates of drug release.[1] These multifunctional materials and herbal-nanomedicines have a more extended surface area, increased solubility, and high bioavailability appropriate for therapeutic targeting.[2] In this state-of-the-art, the constituents of the herbs within herbal nanomedicine formulation govern the medicinal properties. The performance of herbal nanomedicines depends on several active molecules existing in it. These molecules are more proficient to perform all the synergistic actions freely and therefore, these are highly capable to improve the therapeutic efficiency of the HNM.

Nanotechnology configurations used in the designing of the combined herbal-nanomedicine formulation have been governed by the interactions between nanoparticles and herbs. Phyto and herbal remedies are adopted extensively because they have an inbuilt capacity to cure a variety of illnesses with less toxicity with better therapeutic effects.[3] Most of the biologically active ingredients of herbal extracts, such as flavonoids, tannins, and terpenoids, are highly soluble in water, but have low absorption rate, because of their macro sizes. Therefore, they cannot cross the biological barriers (lipid membranes) of the cells. These macromolecules comprise of high molecular size molecules that are inadequately assimilated, hence all of them dispense low biocompatibility and poor efficacy. Thus, the delivery of these herbal therapeutic molecules in the form of medicines is a challenging task because of their poor permeability, and inability to perform in a biological environment, hence resulted in low biocompatibility. These restrictions reduce the chances for the utilization of phyto and herbal remedies as medicine for a good therapeutic impact. The assimilation of novel herbal remedies in nanomaterials diminishes presystolic metabolism, stops the degradation of herbal formulation in the gastrointestinal tract, and accumulation of herbal medicines in the non-targeted tissues and organs. These transformations reduce the side effects and improve the therapeutic efficacy in the long run for patient compliance.[4] Nanoparticles have small size topologies with large surface areas and are very helpful in the assistance of cellular activities. The main worries are the groundwork and utilized stabilization processes for the nanoparticles in the formulation of herbal-nanomedicine because some procedures still need to be established in compliance with scientific standards and to some extent, the chemicals used in these also contribute as reducing agents. These unstandardized formats introduce different new type of constituents and altered resulting interactions that can exacerbate cytotoxicity. While the use of nanotechnology, including the use of nanoparticles in the development of medicines hold excessive potential to improve the diagnosis and therapy. Then, it is important to scale the loose display of the inevitability methodically and harmful chemicals during formulation to withdraw unexpected happenings, side effects, and damaging things.[5] An ideal herbal nanomedicine possesses two topographical factors to perform in different conditions, one of them is the capability to target at least the last one to switch on the herbal formulation at the time of release.[6]

Innovative HNM unlocks new prospects for excellent delivery of herbal-nanomedicine at the right place with the right concentration at the right time and for the exact period including highlighting the stretch of the scientific angle to authenticate the uniformity of herbal medicines. The nature of the ingredients of a herbal-nanomedicine proves their utilization for increasing the bioavailability, biocompatibility, systemic clearance, and decrease in toxicity. These are the essential modifications required for the formulation of a low dose remedy to enhance the outlooks of their clinical uses in the form of herbal nanoformulation. The new herbal-nanomedicines deliver active molecules in sufficient concentration at a specific target during the entire period of treatment. These fundamentals did not match with the earlier utilized herbal remedies and entirely distinctive from the conventional treatments.[7] The targeted drug delivery capacity of the nanotechnology with the combination of herbal therapy can drastically improve the performance of herbal-nanomedicines (figure 1). Further, new advancements of these technologies shed light on characterizing nanoparticles to define their toxicity profiles and enhance the possibilities for their physical utilization and chemical implementation.

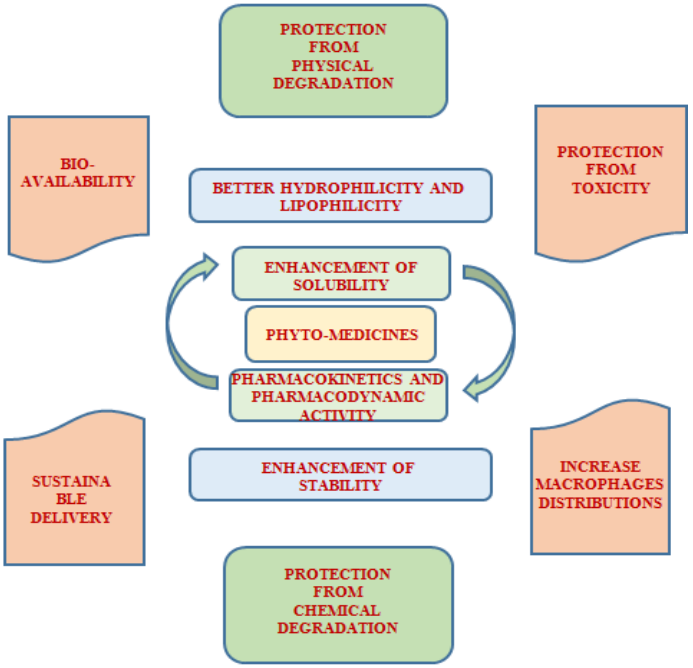

Figure 1. Schematic illustration of various characteristics of phytomedicine and herbal remedies.

Established phytopharmaceutical research underlined the scientific necessities, as the requirement of the nanotechnology in strategies and implementation of different nanoparticles such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursors systems for liquid crystals (PLCs), liposomes, and microemulsions in the development of the herbal nanoformulation to break the hurdles that exist in the path of innovation. Nanotechnology can authorize ingredients with divergent qualities to possess the equivalent formulation and alter substance's features suitable for the biological context. These technological breakthroughs in nanotechnology have refreshed the potential of herbal remedies. The herbal-nanomedicines have the capacity not only to increase the efficacy of active components to achieve better biocompatibility but also to re-establish different ingredients. Some ingredients are not suitable to examine for medicinal applications because they are not fitting and worthwhile to count for this kind of formulation. Besides developing the solubility and stability of dynamic components, nanostructures can spread out a formula action efficaciously to combine active substances with different degrees of hydrophilicity/lipophilicity, bioavailability, biocompatibility, and biodegradability for enhancing the therapeutic index of herbal drugs.[8]

To accomplish the desired therapeutic aim, the herbal-nanomedicine is holding promise for the distribution of active drug molecules in a solidified manner at an optimal flow. As per the bio-pharmaceutical design, the rate and extent of herbal-nanomedicines consumption depend on pharmacokinetics and pharmacodynamics furthermore, their systemic delivery to the body can verify from swift and wide-ranging absorption, or slow or nonstop absorption liable on the simultaneous therapeutic action towards the aspired intention. Nanotechnology is one of the most innovative methodologies for manufacturing of the improved nanopharmaceuticals that can counterfeit the difficulties perceived earlier and thus it can be underlined as green technologies. Herbal-nanomedicine comprises all branches of medications and, thus it is quite capable of focusing strongly on the extraction of herbal extracts to finding out the interrelated chemical engineering routes for industrial preparation as per the requirement suitable to the distinct nature and proportions of the nanomaterials. In this contrast, the fundamental precepts of herbal-nanomedicine performances are the strategies, expansion, and laboratory experiments that can enhance the efficacy of all the biological parameters necessary for the innovation and can generate a non-toxic cellular environment.[9] In this review, the authors highlight the use of theories of phytochemicals in demand for better-quality synthesis and alteration of HNM.[10] The contemporaneous assessment of these therapeutics is a comprehensive appraisal for the innovation of the fresh advances capable of the designing of novel HNM. This up-gradation is based on the specific and extremely conferred theories of interactions between nanocarriers and herbs or phytomedicine. Subsequently, the highlights of the herbal-nanomedicines expansion will place in the future to sense the needs. There are different concerns in field of nanotechnology that need to look over towards the eventual widespread use of phytochemicals in the formulation of herbal-nanomedicine to treat a wide range of diseases efficiently.

HISTORY AND USES

During the ages, humans depend on nature for their essential needs, food, and even medicines. Human is naturally growing herbs, and employing herbal remedies for the treatment of a wide range of diseases.[11] Carbon dating from ancient Babylon (Iraq) registered that the plants farmed for medicinal uses 60,000 years ago. Reproduced material on the use of the herbs and herbal extracts for medicinal purposes evidenced roughly 5,000 years in India, but the best-known proof existed in Egyptian pharmaceutical records "Ebers Papyrus" which is containing more than 800 formulae of gargles, snuffs, poultices, infusions, pills, and ointments with beer, milk, wine, and honey usually utilized as drugs. Other 700 different herbs, medicinal plants, i.e. acacia, castor oil, and fennel, were also included as a source of medicine. These formulations and extracts contain specific chemicals (iron, sodium chloride, and sulfur). Herbs and herbal extract-based models of the sophisticated and classical medical models are in practice with the most advanced credentials dating from 2600 BC ago. The documenting proofs evidenced around 1000 plant-derived substances used for medication in Mesopotamia. The Egyptian medicine distinguished document "Ebers Papyrus" that evidenced the recording of 1500 BC. Ayurveda is an Indian system of medicine approximately evidenced five thousand years old.[11] Furthermore, documentation of the Indian Ayurvedic[12] system dates from before 1000 B.C. (Charaka; Sushruta and Samhitas with 341 and 516 herbs). The Greeks and Romans contributed substantially to the rational development and the use of herbal medicines in the ancient Western world. Dioscorides, a Greek physician (100 CE), accurately documented the collection, storage, and use of medicinal herbs during his travels with Roman armies which revealed to the world whilst Galen in (130-200 CE.). Another practitioner and teacher of pharmacy and medicine in Rome is well known for his elaborate prescriptions and formulae employed in combining herbal medicines.[13] The Arabs, however, preserved much of the Greco-Roman expertise during the Dark and Middle Ages (5th to 12th centuries) and expanded it to comprise the use of their resources, together with Chinese and Indian herbs which were unknown earlier to the Greco-Roman world.[14]

Chemical scrutiny first turns out to offer the extraction and modification of herbal ingredients[15] in the early 19th century. However, the recent phytopharmaceuticals analysis interprets the scientific essentials for herbal medicines which have similarities with the modern medical system capable of extending technique for exhibiting novel formulations[16]. Nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, SLNs, are the key resource as required for the innovation of HNM.[17] Many of the current nanomedicines (liposomes, polymeric micelles, nanoparticles, dendrimers, and nanocrystals) are the portions of the orthodox ancient medication approach in the nanometer range in the 1960s. Relatively other nanoparticles and dendrimers innovated in the 1970s. The significance of nanotechnology in the improvement of herbal remedies is an approach that can manipulate drug molecules chemically and supramolecular arrangements for generating tools for specific tasks.[19] Nanoformulations decrease the particle size and increase

the surface area to enhance the bioavailability, and reduce the side effect of herbal medicine which is useful for the treatment, diagnosis, monitoring, and control of biological systems recently expressed as herbal-nanomedicine. The role of nanotechnology is upgrading and furnishing the bioavailability, biocompatibility, and biodegradability herbal nanomedicine i.e. nano curcumin from Curcuma longa, nano vincristine from Vincarosea, Podophyllotoxin from Podophyllum hexandrum,[20,21] Taxol from Taxus plant etc..[22] Therefore, the nanomedicines transformed and developed[23] into biologically active herbal nanomedicines.[24]

NANOTECHNOLOGY TO ENHANCE THE THERAPEUTIC INDEX OF HERBAL MEDICINES

Nanotechnology will categorically influence the herbal medicinal research, predominantly related to the bio-distribution of novel phytomedicine, and to enhance the manufacturing processes employed in the preparation of the herbal nanomedicine shortly. The HNM development is based on the origin of the interaction between the herbal and nanomaterials. These interfaces exhibit increased therapeutic significance by reducing the toxicity and side effects of herbal remedies with improved efficiency and high grade of bioavailability.[25] Bio-distribution nurtured herbal-nanomedicine formulation by (1) stabilizing the physical and chemical degradation (2) by stopping the decomposition of formulations (3) by evaluating the adopted methods for the preparation (4) by suggesting types of active ingredients, their size, (5) entrapment efficiency (6) by proposing new concerning routes of administration and (7) by providing new applications of novel formulations. These are the key points to be covered necessarily for boosting the novel formulation of the herbal-nanomedicine. The bioavailability of the active constituents of the herbs is another region of plentiful distinction. Phytomedicine and herbal remedies possess a significant therapeutic efficacy that must examine to enhance the therapeutic index of HNM by the use of nanotechnology. Different varieties of literature testified impact of the phytomedicine for getting an excellent command of in-vitro bioactivity. But the poor aqueous solubility, larger molecular size, high degradation in gastric medium, and at the time of extensive metabolism are the gray areas. Because of these hurdles, these phytomedicines cannot be considered as a potential candidate for a novel therapeutic. These are the genuine difficulties, which confine the advantage of these plant extracts to be used as medicine for in-vivo.[26] Verities in the size of nanoparticles provide a high surface-area-to-volume ratio and as a result, more and more water molecules can mount the particles for enhancing the solubility of the hydrophobic compound (figure 2). The herbal extract comprises many larger macromolecules having different chemical properties that can neither absorb directly nor swiftly incorporated. Nanotechnology is capable to make these macromolecules accessible for their biological utilization by absorption.[27] Phytomedicine can play an important role in the in-vitro activity, but these are less effective in-vivo because they have poor water solubility and lipophilicity. The molecular sizes of these molecules were considered inappropriate to incorporate in these formulations and not suitable for absorbing and thus it has poor systemic availability.[28]

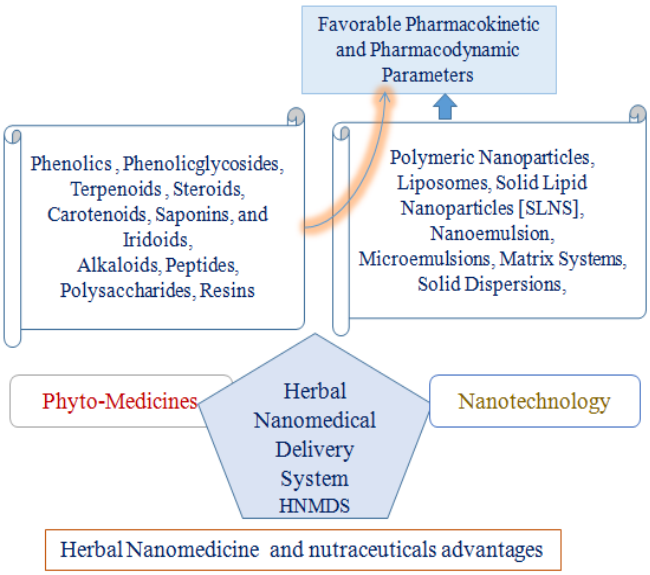

Figure 2. Schematic illustration for reviewing characteristics of nanotechnology to enhance the pharmacokinetic and pharmacodynamic activity of phytomedicine and herbal remedies.

A better understanding of the biopharmaceutics and pharmacokinetics of phytomedicine can help in the rationales designing of the dosage regimens. By a proper investigation, it is easy to analyze the herbal-nanomedicine formulation by incorporating it into the nano-based formulation to avoid any physical and chemical degeneration[29] during the implementation and the formation of HNM. The mechanisms occurred at the time of the distribution of HNM is an important factor for better performance. This is achieved by incorporating the herbal medicine in the multifunctional nanomaterials to re-design the desired formulation of the herbal nanomedicine at the molecular level.[30] These distinct topologies of herbal-nanomedicine are there in the drug formulation at the nanoscale intending to plan the formation of a novel drug with unique capabilities. These formulations have different shapes, sizes, compositions, and functions that are capable of making changes chemically/physically for better interaction with specific properties of both herbal-medicines and phytomedicine. These physiochemical characteristics reliant on the features of the herbal source to elaborate and enrich the pharmacokinetic and pharmacodynamic activity for matching with the targeted organ with a high grade of hydrophilicity or lipophilicity and specific bioavailability.[31]

Nanotechnology has the potential to deal specifically with the negative consequences of the herbal-nanomedicine up to a certain limit and enhance its formulations into more target specific remedies with high efficiency. Therefore by exploiting the nanoformulation, and concerned encapsulation routines, it is conceivable to design the desired therapeutic.[32] For these kinds of objectives, the nanoparticles were designed and prepared in different manners having various shapes and sizes. It was evident during the utilization of several compositions for the proper

functionalization to change the specific properties of the nano herbal formulation physicochemically. This kind of methodology is elaborating the characteristics of the herbal nanomedicine to get succeed to target the diseased cells. Besides organic nanoparticles as detailed earlier, the inorganic nanoparticles, e.g., gold, silver, zinc, copper oxide, aluminum oxide, iron oxide, ceramics, and carbon nanoparticles were also employed for the consideration of the phytochemical and herbal remedy formulation. Inorganic nanoparticles are of three types, transition metal nanoparticles, ceramic nanoparticles, and carbon nanoparticles.[33] These herbal nanomedicines have better selectivity, high grade of solubility, fit for specific target delivery safely, better effectiveness, and very useful to decrease the frequent dose. The herbal nanomedicine enhances the entire surface area of the formulation because of the small size of the nanomaterials. Therefore, the HNM is highly capable of assigning an active role during the diffusion process in the blood, to reduce toxicity, and to deliver high therapeutic effects. The enhanced penetration and retention power of the nanoparticles can cross the blood-brain barrier easily for better impact.[34] However, most of the herbal remedies are insoluble and have lower bioavailability, not have increased systemic clearance requirement and echoed order, or it required a higher dose. These parameters do not allow to consider herbal remedies as better therapeutic agents. Therefore, these remedies considered as a poor candidate by the physicians and never recommended for therapeutic.[35]

In new phyto research and development, the formulation required for a nano dosage comprising different nanoparticles (polymeric nanoparticles [nanospheres and nanocapsules], liposomes, pro liposomes, solid lipid nanoparticles, and nanoemulsion) that is a torturous task.[36] Most of the herbal extracts instability and speedily degrade in biological environments and it reduced activity. Encapsulation of such herbal extract in nanomaterials outfitted them to protect from the harsh conditions to avoid any decomposition.[37] For example, quercetin has a lifetime of only five minutes in plasma, and whereas quercetin loaded in liposomes with better-quality polyethylene glycol (PEG) has a lifetime of over five hours in plasma. When quercetin is encapsulated in polymeric nanoparticles, it inhibits antioxidant activity. When it encapsulated in nanoparticles (polymeric nanoparticles), enhanced stability observed.[38] It also evidenced that the polymeric nanoparticle improved the stability of the herbal-nanomedicine in an acidic medium. However, the polymeric nanoparticles released the antioxidant under neutral to basic conditions, making such herbal nanomedicines fit for oral delivery. Some biological active compounds utilized to protect and deliver herbal nanomedicine ahead of the acidic conditions in the stomach.[39]

NANOCARRIERS FOR HERBAL EXTRACTS DELIVERY

Nanotechnology deals with many problems and can overcome them by suggesting solutions, for example, the use of nanocarriers in herbal formulations and encapsulation of insoluble compounds in nanoparticles.[40] This methodology has the potential to innovate several HNM formulations for clinical trials and their further implementation. Nanotechnology is quite useful in the delivery of herbal remedies having a poor bioavailable, improper physicochemical characteristics, low therapeutic index, improper pharmacokinetic, and pharmacodynamic parameters.[41] Apart from it, these formulations are capable to improve the bioavailability of herbal-nanomedicine. Therefore, there is a need to improve the targeting capacities of these remedies to release the required dose of the HNM. If, it required some modification in the topology of the traditional nanoparticles as well in the ligands to increase the therapeutic index of the HNM for lowing side effects, were being done. There are a lot of advances in using nanotechnology in the herbal nanomedicine formulation and also in improving the essential deliveries to the target sites.[42] Researchers can itemize the emerging trends in nanotechnology for convincing and discussing the difficulties as well as the controversies allied. It is possible to use the potential of natural ingredients and remedies for the advancement of HNM formulation technically. By using nanoscale materials, the therapeutic value of natural products can drastically enrich for antimicrobial defense. However, few of the multifunctional nanomaterials or herbal extracts are not fit for the formulation of the herbal nanomedicine, specifically those which have no good pharmacokinetics, pharmacodynamics, and therapeutic index. For the formulation of a higher dose of the herbal nanomedicine, it is quite possible to craft the nanocarriers on a larger scale, but this will be questionable and impractical during their utilization.[43]

Most of the biologically active constituents of extracts are highly soluble in water, but have low absorption, because of it, they are incapable to cross the biological barriers that existed in the cell membranes. All of them have high molecular size, and hence they were poorly absorbed. It resulted in a decrease in bioavailability and efficacy.[44] Some of the extracts did not recommend for the clinical use because of these obstacles, as cited above. Nanotechnology explores the possibilities by mixing nanoparticles with the herbal remedies and recommends these nanomaterials for the formulation of HNM. These multifunctional nanomaterials are capable to deal with the plant extracts to reduce the necessity of high dose, and side effects, for improving biological activity.[45] Nanotechnology develops such conclusions for controlling the matters in the 1-100 nm range. Hence, at this scale, the materials showed unique physicochemical properties including ultra-small size, large surface to mass ratio, and high reactivity. These nanoparticles have high capabilities and consider a unique option for biological interactions. The particle size and surface characteristics of nanoparticles are useful in the herbal nanomedicine formulation and enhance the therapeutic index.[46] Nanoparticles have the potential to contribute to herbal therapies for the delivery of an excellent amount of herbal formulation at the targeted location. This herbal nanomedicine capable of suitable action because all of them overcome all the biological barriers i.e. acidic pH of the stomach, liver metabolism, and increased prolonged circulation in the blood.[47] Natural product's efficacy restricts metabolism and medicinal activities because of their low hydrophilicity, intrinsic dissolution rate, physical and chemical instability.

Furthermore, few of the macromolecules affect the biological and medical parameters of the herbal-nano formulation. Such

formulations initiate and display uneven absorption, poor pharmacokinetics, and low bioavailability, infrequent bio-distribution, disrupted first-pass metabolism, influence slight penetration, low accumulation observed in the organs of the body, dispense low targeting efficacy and the same were identified by the clinician during the clinical trials.[48] Novel nanoformulations as nanoparticles, micelles, and vesicles recommended for the HNM formulation that can contribute, rectify, and enhance the significant commitment in overcoming the limitations as specified earlier.[49] In comparison of it, with a crude herbal extracts, nano-sized medicines, and their antimicrobials derivatives hold many advantages. These composites, or mixtures have the potential to enhance composite solubility, prescribed in small medicinal doses, and finally, these HNM displays a better-quality absorbance. Nanoscale herbal-nanomedicines have bioactive molecules and biodegradable nanoparticles[50] and thus it has a high bioavailability,[51] solubility, retention time, efficacy,[52] specificities, tolerability, and therapeutic index.[53] Nanoscale herbal nanomedicine reduces the patient's expenses, as well as the risks of toxicity. On the other side, these formulations display numerous advantages as they are capable to protect premature degradation, enhance intracellular penetration, and better interaction under biological conditions.[54] Nanoscale size leads to better solubility of components, and a decrease in the amount of the dose required. These nanoscale remedies are capable of enhancing the absorption of the active ingredient. [55] The herbal nanomedicine improves surface-to-volume ratio and changes the crystalline form to promote the designing of the novel nanomaterials. These biophysical parameters influence the specific release and act as a booster by reducing the systemic side effects.[56] During the delivery of the herbal nanomedicine in the blood capillaries, these tiny sizes deal with the problems emerged in their territories. Despite it, this herbal nanoformulation exhibit excellent bioactivity.[57-58] Phototherapeutic acquiescence is a scientific demand and a key to the delivery of different components at the diseased site for a speedy recovery. To avoid the general complications inhibit the treatment, HNM intensifies the interactions with biological components. HNM did not only moderate the frequent administration to reduce compliance, but also benefit to enhance therapeutic value. These methodologies are capable to reduce toxicity and enhance bioavailability. The nanoscale remedies have the potential for enhancing the activity to deal with the hurdles that existed in the development of herbal nanomedicines (figure 3). This is conceivable because of the capacity of nanocarriers which can protect the encapsulated herbal nanomedicine molecules and easily transport them to various areas of the cell types of machinery. To improve the capability of the nanomaterials by any means i.e. by increasing concern selectivity and efficacy, by protecting it against any thermal- or photo-degradation, by reducing side effects, and by controlling the release of active constituents, before the nano-herbal formulation used therapeutically these changes must employ to them for transforming it into more effective and attractive therapeutic.[59] The advances in recent decades regarding herbal nanomedicine development,[60] are the vital necessity. The progress of nanoscience and nanotechnology is capable to re-count and address the use of nanoscale materials[61] in the development of HNM.[62]

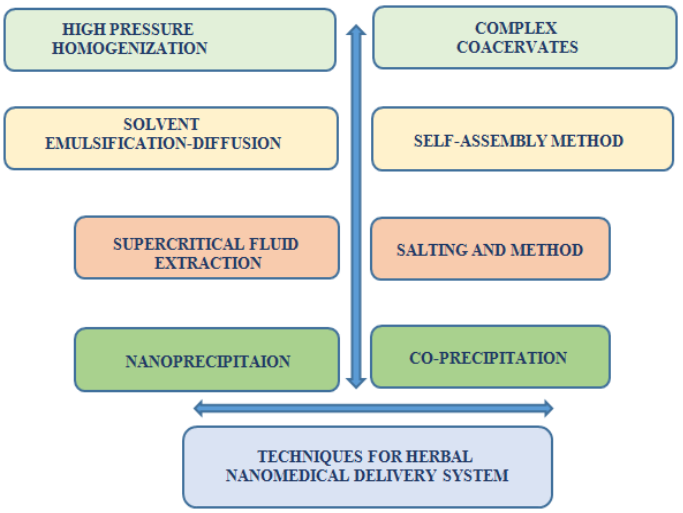

Figure 3. Schematic illustration for selectivity and efficacy of herbal nanomedicine.

HOST-GUEST CHEMISTRY INTERFACES AND CHALLENGES OF HERBAL NANOMEDICINES

The mechanism of the formation of interfaces happened in herbal nanomedicine to control the feasibly that required to stimulate the phase sequence, chemical, and physical characteristics of the eluding faces.[63] Hence, it is foreseeable that the essential principle of herbal nanomedicine interface and interaction phenomenon occurred between the nanomaterials and drug molecules. The reasonably interlinked and associated features of herbal-nano remedies are the main components of their profile, dimension, and nature of herbal extract. These features originate and explore the possibilities for the formation of an interface.[64] The novelty existed in the herbal nanomedicine interfaces already at the time of designing[65] of a novel HNM. These nano-herbal formulations are capable to cure the fatal diseases such as hypertension, diabetes and dyslipidemia, malignancy, and respiratory disorders. Several well-known mechnism[66] and formulations are summarized to disclose the various features of the herbal nanomedicine to discover more feasible interfaces for the innovation of novel remedies for the proper treatment.[67] Herbal nanomedicines interface evolution occurred naturally and frequently during the herbal nanomedicine formation, modification, and alteration. These nano-herbal formulations can hit the target site and capable to participate in the metabolic pathway to increase the herbal nanomedicine[69] impact and extension. So many factors are there that can affect the impact of the herbal nanomedicine during the healing and ongoing interrelated pathways. The diversity, host-defense variability, genetic shift, and drift phenomenon of the HNM are the main causes to be underlined for a proper rectification and to enhance the effectiveness.[70] For extending the surface specificity of the bio-transformational pathways of physiology, there is a need to outline the foremost involved circumstances responsible for distinct interfaces among herbal, nanomaterials, and food. The capability of different chemical

moieties to interact with receptor locations for changing the physiological environment that influence the pharmacodynamic of herbal-nanomedicine interfaces[71] underlined for the interpretation. Whereas the pharmacokinetics and pharmacodynamics interfaces leave an impact on the transform immersion to generate interference in the distribution.[72] These exercises are crucial to outline the difficulties in the implementation processes and detect the competition in theme metabolic and excretory pathways.

The fundamental mechanism of the pharmacokinetics, and pharmacodynamic of HNM as an internal interface is to induce or inhibit the intestinal and hepatic metabolic enzymes as per the needs.[73] Few of the mechanisms and components of the pathways for the recognition of the biologically active complexes and the metabolites form of the crude extract are exposing a bioassay pattern of the unique immune effective fractions. These are vital mechanisms and pathways are known for the therapeutic efficacy for the proper expression of the biological activities in many pharmacological[74] and toxicological trials. The therapeutic index of the HNM governed the patterns that existed during the alterations phenomenon in the gastrointestinal functioning. These parameters control several other features of the herbal nanomedicine such as absorption, inference, inhibition of metabolic enzymes, transportation of proteins, modification of renal secretion, and the metabolic activities.[75] The intrinsic pharmacological properties of phytochemicals[76] and the therapeutic index of HNM hold the nobility of the proposed formulation. These effects could be synergistic, additive, and antagonistic depend on the formulation of the novel HNM. Such herbal remedies comprise a multifarious combination of pharmacological active phytochemicals,[77-78], and most of them are secondary metabolites,[79] acetate-malonate, and acetate mevalonate pathways. These phytochemicals consist of phenolics (such as tannins, lignins, quinolones, and salicylates),[80] phenolic glycosides (flavonoids, cyanogens, glucosinolates), terpenoids (such as sesquiterpenes, steroids, carotenoids, saponins, iridoids), alkaloids, peptides, polysaccharides (gums and mucilages), resins, and essential oils and frequently interface with nanomaterials.[79] These interpretations of assumptions enhance the chances of the formation of clinically satisfied herbal-nanomedicine interfaces. The objectives of the treatment performed during the evaluation of the clinical consequence happened during the herbal nanomedicine interfaces as a poise necessity to conflict between inflated nanotoxicity and decreased efficacy.[81] When the herbal remedy interface with multifunctional nanomaterials often evidence clinical equivalence, subsequently, the mechanism may power both the time sequence and tactics of dodging the interface.[83] The etiology and clinical repercussions of herbal nanomedicine interfaces are multifactorial and principally volatile, to embrace inpatient and determinants of the herbal nanomedicine[84] as referred earlier. A rational analysis of mechanisms of herbal nanomedicine[85] interfaces is decisive to forecast their clinical significance. This is the only method adopted by a clinician to scrutinize[86] new conclusions scientifically (figure 4). There are some other uniform mechanisms to come across usually, but a rarity, comparatively to these mechanisms which exceptionally happen during the herbal nanomedicine interface.[87]

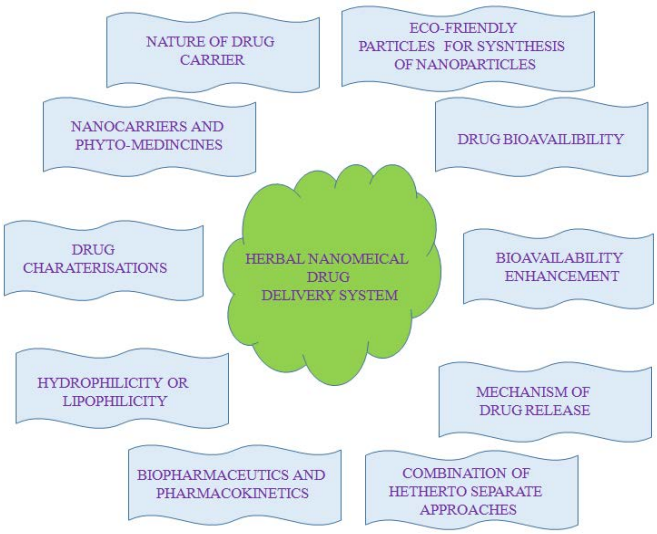

Figure 4. Schematic illustration of active ingredients of herbal nanomedicines components i.e. interaction modification, alteration of the target site, and metabolic pathway to reduce accumulation.

There are many kinds of the interface within the formulation of the herbal nanomedicine: a few of them are (i) herbal extracts interface with nanomaterials, (ii) herbal extracts interface and absorption patterns, (iii) herbal nanomedicines and transportation interfaces, (iv) herbal nanomedicines and distribution interfaces, (v) herbal nanomedicines and metabolism interfaces, (vi) herbal nanomedicines and elimination reactions interface, (vii) herbal nanomedicine and disease interfaces, (viii) herbal nanomedicine and food/nutrients interfaces, and (ix) herbal nanomedicine and environment interfaces.[88]

HERBAL EXTRACTS INTERFACE WITH NANOMATERIALS

Herbal nanomedicine interfaces are influenced by the varieties of nanomaterials and herbal extracts. It is a quite noticeable phenomenon, and significant character requires performing the verify roles for lowing the toxicity to increase the therapeutic index. These are the significant alterations that referred to the relatively unstable herbal remedies and nanomaterials ratio utilized in the formulation. These phenomena have an impact on the clinically unique confrontations and the outcomes. If there is any impurity exists in the fitting dimension of herbal nanomedicine interfaces, then it can lead to clinical implications by disturbing the novel ratio necessary for the formulation. Therefore, it depends on the seriousness of diseases require for the treatment. If these issues do not resolve, then it will be lethal for the novelty of the herbal nanoformulation.[89] The confrontation of the herbal nanomedicine influence the existence of the interfaces responsible for the enhancement of the therapeutic index chemically or biochemically.[90] Consequently, these mechanisms are typically accountable for contrary effects allied with herbal nanomedicine interfaces. For example, one herbal nanomedicine

formulation distresses[91] pharmacokinetic profile, therapeutic values, and phytochemical parameters. It can disturb the other phenomenon i.e. absorption, distribution, metabolic biotransformation, excretion or elimination of anyone, and mechanism of the interfaces[92]. These happening degrade the receptors' potentiality. These are the few notable factors that can interfere or transform clinical responses and implications. There are many mechanisms named pharmacokinetics and pharmacodynamics interfaces wherein the herbal nanomedicine governs the interaction and concerned reaction events. It assesses that the pharmacokinetics and pharmacodynamics interface are necessary at all expenses from the perspective of their clinical significance. The probability of an herbal nanomedicine formulation to assist with a common metabolic pathway[93] does not mean that it is a clinically noteworthy interface. Every time, herbal-nana formulation co-administered, these interfaces are being[94] reliant unitedly on many dynamics. The abilities of the novel herbal nanomedicine to perform in the binding locations or act in the presence of the metabolizing enzyme, effectively.[95] It also depends on the concentration suitable for binding.

Furthermore, the identification of the interconnected pathways concerns with the elimination of herbal nanomedicine that can incline or decline the feasibility necessarily for a substantial pharmacokinetics interface. Hence, there is a need to pretend these interfaces, so that the intra-patient dissimilarities cannot allow to temper the various parameters (acclaimed quantity and permission, conducted capacity, the rate and extent of absorption, the plasma concentration, distribution, metabolism, elimination, site of action, genetic variations and the enhance the receptor) of the herbal nanomedicine as a treatment regime.[96] The noticeable elements of the outlook of the herbal nanomedicine are physiological and pathological variations that happened through the organ function.[97] The parameters of the pharmacodynamic interfaces impartially united in recurrence to identify the clinical effects of the precipitant herbal nanomedicine entity at the site of action. The herbal nanomedicines proceed with similar pharmacological or identical effective manners during their comparable disposal to act. The different analysis outcomes were observed constantly as a synergistic or emergency response. The two herbal nanomedicines may or may not routine on the same receptor, and these processes strengthened or influenced the clinical effects.[97] The synchronized effect of two herbal nanomedicines can intensify renal damage, where the dose of herbal nanomedicine is inadequate to generate toxicity. Certain pharmacodynamic interfaces occur regularly wherein the toxic components of the therapeutic material of herbal nanomedicines did not associate with the unconnected divisions of a combined route to execute a nonstop response.

HERBAL NANOMEDICINES AND ABSORPTION INTERFACES

Eventually, the oral path is one of the frequently used options adopted for the delivery of the herbal nanomedicine, wherein the gastrointestinal features interrupt a better-quality absorption.[98] The absorption of an herbal nanomedicine blocked by many macromolecules existed in the herbal remedies, which disturb the concerned interfaces of the clinical prominence. These events create a terminal impact on the effectiveness of the herbal nanomedicine. These phenomena influence the rate of results and alter the level of absorption. The amount of the herbal nanomedicine dose is most important for frequently employed. The fixed amount of the dose showed a significant improvement in chronic illness. When two dissimilar formulations of the herbal nanomedicine considered in high concentration, again, there is a possibility of a successful output observed clinically.[99] Therefore, it will more vital to detect alterations in herbal nanomedicine absorption. These results also vary because of the variations that occurred in gastrointestinal pH. The mechanism of the absorption of the herbal nanomedicine solely depended on various factors such as the gut pH, lipid solubility, pKa of herbal nanomedicine, and action of the P-glycoprotein. During the fluctuations in gastric pH induced by H_2 and proton pump blockers, the antacids comprising metals pointedly diminish herbal nanomedicine bioavailability. During the clinical exercises, the rate of determination of the absorption phenomenon is left undefined. It is because other compounding effects such as chelation and gastric motility did not include in the analysis.[100] However, the variation in pH has committed clinical implications and directly influences the absorption of herbal nanomedicines. Most of the herbal-nano formulations are insoluble in water and ionized only at low pH. Therefore, gastric acidity is a crucial factor in the therapeutic index and originated interfaces. Variations in the absorptions are influenced by chelation and adsorption of many convincing herbal nanomedicines and interconnected interfaces. These phenomena occurred because of the alterations in herbal nanomedicine absorption. The best clinically significant interfaces materialize just because of chelation or the formation of insoluble complexes. This can also happen when herbal nanomedicine regains stability to neutralize the bile acids. Clinically important interfaces expose the insoluble herbal nanomedicines in the presence of the chelates and metal ions. The gain of the standard antimicrobial effectiveness for these nano-herbal remedies are the main goal. Chelation executes a significant extent in fastening the bioavailability and antimicrobial properties of the herbal nanomedicines obtained by phytochemicals.[101]

HERBAL NANOMEDICINES AND TRANSPORTER BASED INTERFACES

Herbal nanomedicines and metabolic interfaces are the furthermost imperative to be scrutinized excessively for more scientific details.[108,103] Observed scientific particulars and interconnected features of the expansions mostly concerned with the dealings with the CYP450 enzymes. The concerned scientific interpretations have transfigured in the learning of herbal nanomedicines interfaces along with their impacts. The human body endlessly unprotected from the foreign materials, those are not originated naturally in the body. These existed abnormalities tempered the body functioning and as a result, it attained a therapeutic end. These transformations are governed by a plethora of enzymes. These facts revealed that the impact of these enzymes actively governed various mechanisms and biological activates induced by the herbal nanomedicines inside the body. During these activities, several wanted and unwanted changes occurred.

Overall, some of the inactive components transformed into active forms or later one some of them converted into the toxic metabolites during biotransformation.[109] Most of the metabolisms activities are induced by herbal nanomedicine which are essential and having the potential require to influence the receptor activities during the action at the diseased sites. The concerned consequences related to prerequisite lipid components infiltrate through the lipid plasma membrane barrier.[110] These transformations were analyzed in various steps, as in phase I, it was noticed that the oxidation/reduction reactions refurbish the outputs on the topic of herbal nanomedicines. During the phase II analysis, the mechanisms of the conjugation/hydrolysis reactions addressed the transformation of glucuronic acid and glucuronyl transferase. These exercises were done to find out the alterations existed in the formulation and activities of HNM. These phenomena also deal with the inactive composites to lead their evacuation. These herbal nanomedicine having a short half-life, inactive metabolites, and poorly absorbed counterparts. However, these parameters are lowering the therapeutic index, which inhibits the clinical perspective and yield more toxic components. These unwanted happenings distress metabolic activities in the body competitively to the other interconnected phenomenon.[111] The interfaces related to the herbal nanomedicines and concerned metabolism can easily increase or decrease the impact of the herbal nanomedicines on the diseased cells and organs. Inhibitors are the other components of the cellular environment that can directly influence the action of the HNM for a particular enzyme. These pathways render the activates of the heart towards the optimal level of metabolism.[11]

HERBAL NANOMEDICINE AND ELIMINATION REACTION INTERFACE

Exist paths for the exclusion of herbal nanomedicines go through the kidney and bile. There is no substantial herbal nanomedicine that interfaces through bile abolition. These remedies are mostly evacuated by the kidneys and initiated the alterations in various interfaces of the cellular environment. The mechanisms of these transformations have a rivalry at active transport locations. It can be observed from the shifts in Glomerular filtration, passive renal tubular reabsorption, or active secretion and urinary pH. The renal tubules hold the vital excretion pathway. Some features of the herbal nanomedicine hamper the renal excretion. These are the desired necessities for the existence of these interfaces at the active transport locations.[113]

HERBAL NANOMEDICINE AND DISEASE INTERFACE

Herbal nanomedicine and disease interface occurred during the medication of a disease. The clinician must analyze the patient's disease profile to strategize a suitable therapeutic regimen. These predictions are prudently matching with the necessity of the safeguard, and help to find out suitable medicines to shield from the disease ailments. The herbal nanomedicines have different therapeutic types and they may or may not have any inconsequential potential. These parameters can influence the herbal nanomedicines and disease interfaces.[114] The herbal nanomedicines are proficient in intensifying critical and chronic diseases. Herbal nanomedicine and disease interface occurred during the interaction of the beta-blockers used to treat hurried asthma, peripheral vascular disease, and the insignia of hypoglycemia. Few more interfaces also occurred during the treatment requisite for certain diseases i.e. psychiatric disarrays autoimmune disorders, G.I. diseases, respiratory and infection.[115]

HERBAL NANOMEDICINES AND NUTRIENTS INTERFACE

Natural products, natural compounds, microorganism-derived compounds, and their derivatives used in medicine and are in high demand, because they showed great potential as therapeutic agents in the treatment of cancer, microbial infection, inflammation, and other disease conditions. The incorporation of nanoparticles with these components derived from the natural sources has higher therapeutic effects. These herbal-based nanosystems have promising proficiency in the treatment of various diseases. Besides all, there are so many nutrients that exist in these resources to boost the therapeutic effect and the immune system.[116] A deficiency of calibration and adulteration further pay to these interfaces. The mechanisms of food-induced interfaces are essentially identical as herbal nanomedicines interfaces, however, these happenings befall because of variations in absorption and may damage their nutritional components. These alterations may occur due to transforming metabolism.[116]

HERBAL NANOMEDICINE AND ENVIRONMENT INTERFACE

The pharmacokinetic and pharmacodynamic parameters concerned with the interpretation of the herb-drug interface. These analyses have shown signs by interconnecting the diffident mechanism, and their nature for the manageable confirmations. With the growing interest in the development of the herbal nanomedicine, several concerns are there for covering the pharmacological activities, and the other parameters of the therapeutic index. These underlined features must permanently address in the clinical safety assessment trials conducted during the exercise of the upgrading of the formulation of herbal nanomedicines. Sometimes, the herbal nanomedicine mixtures can yield small therapeutic results due to some undisclosed factors. The illustrated schematic brick model of nanomedicine and phytomedicine displayed various segments of the therapeutic index of HNM, such as the effectiveness of pharmacokinetics, mechanism of action, site of action, and the accurate dose ratio. Herbal nanomedicines metabolize enzyme transporters. Notwithstanding, these features associated with the effectiveness of the herbal nanomedicines interfaces, and further analyzed for forecasting about these imaginary interfaces. Therefore, the methodologies applied to explore the impact of the herbal nanomedicine interfaces to endure the objective of the pharmacotherapy. The evaluation of the herbal nanomedicines and its interface with the concerned disease is an important factor to analyze because it can explore the predictability of the nanomaterial-composition, ambiguity, if any in the constituents, along with the impact of the relevant constituents on the pharmacokinetics. [117] The output of these analyses is additional feature that can alter the existing lookout persist in the herbal nanomedicines guideline. Researchers of the different streams are

putting their best efforts to design the novel models of the nanomaterial to prove and test the pharmacokinetics of distinct herbal components to facilitate the forthcoming credentials of herbal nanomedicines interfaces. The theme of such research can grip the capacities to search decisive evidence regarding the potential of the HNM that will be useful for both patients and clinicians. Finally, these efforts pointed out existed peril during the utilization of the HNM for orthodox pharmacotherapeutic treatments.[118] Herbal nanomedicine interfaces deal with the plasma herbal nanomedicine concentration for interacting at receptors on target organs and concerned mechanism[119] holding single molecules entities for chemical transformation. Essentially all these phytochemicals contain the combinations of pharmacologically active ingredients and constituents. Most of the herbal[120] nanomedicines interfaces, the cytochrome P450 (CYP450) system, and the herbal nanomedicine transported P-glycoprotein (P-gp) perform a significant role in all the interlinked mechanisms associated with inactive ingredients.[121]

ADVANTAGES OF HERBAL NANOMEDICINES DELIVERY SYSTEM

Herbal nanomedical deliver system transports the herbal formulation directly to the diseased cell/site of action in the form of herbal-nano formulations and perform as a novel drug delivery system. It is convenient and has more benefits as compared to other medicines currently in the practice. The HNM can deliver the active constituent as per the desired concentration during the entire treatment period by directing it to the preferred site of action. Conventional treatments do not fill these requirements which are very much required for successful targeted drug delivery. By using nanoparticles (liposome, ethosome, phytosomes, emulsion, microsphere, and solid lipid nanoparticles) for carrying the HNM for transportation has enriched the therapeutic effects of these herbal remedies and the phytochemicals. The HNM[122] formulation has inbuilt features that matched with the requirements necessarily and persisted in the novel drug delivery system. To achieve it, there is a need for special inbuilt features in HNM formulations which are capable of displaying the impact on the site. Such inbuilt features enhanced the required bioavailability and biocompatibility. Whenever the chemical activities of the extracts increased instability within the HNM formulation, if it is, then it is quite capable of initiating the persistent release of drug molecules without any toxic effect and a result, a better-quality therapeutic efficacy succeeded. The primary purpose of developing alternates of the herbal remedies to enhance the efficiency and efficiency of drug molecules with increased safety during the drug delivery for proving a better therapeutic effect on the patient. However, the advances of phytopharmaceutical research can cope up with the scientific desires (determination of pharmacokinetics and pharmacodynamics mechanisms, identification of the diseased site, and the measurements of the accurate dose ratio) necessary to transform and incorporate herbal remedies in nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles to prepare HNM as a novel therapeutic, [123] and illustrated in figure 5. Therefore, there will several benefits utilizing the HNM such as increased efficacy, and efficiency with a better therapeutic index. The transportation of herbal nanomedicines molecules, mainly made from the distribution of influx and efflux transporters for which they are substrates.[124] The transporter-mediated disposition of small-molecule enables tissue targeting capability of adding a second small molecule. It will keep going on till there is a need. These procedures have no inhibitory pharmacological effect to influence the expression of carriers present within the herbal nanomedicine.[125]

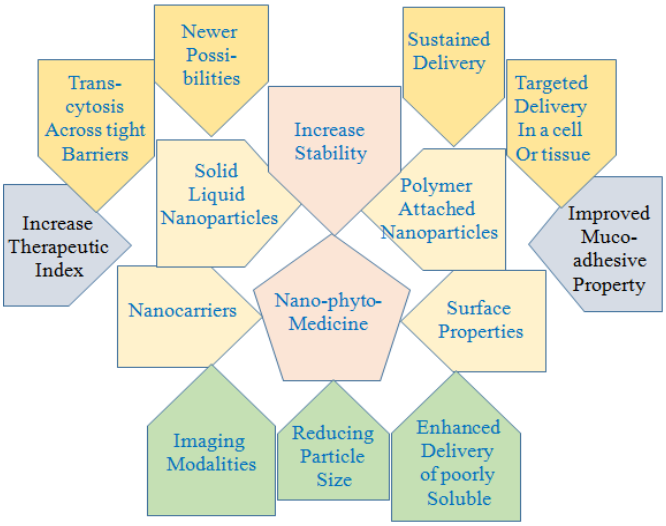

Figure 5. Schematic brick model of various features of herbal nanomedicine and phytomedicine i.e. the effectiveness, determination, pharmacokinetics, mechanism of action, and site of action.

Notwithstanding, how an HNM transpired through binding or chemical interaction and why the concentration of HNM at the site of action displayed impacts. The relationship between HNM dose and ingredient ratio can be established without differentiating the impact of the route adopted. Comparatively, the concerns of HNM concentration at the cellular level are an even more complex phenomenon. The relation of the dose and corresponding response must reflect the implementation of the principles of pharmacokinetics and pharmacodynamics applied in determining the essential dose frequency and the therapeutic index.[126] One of the features of the therapeutic index is the ratio and the minimum toxic concentration to the median effective concentration. These parameters helped in the determination of the efficacy, efficiency, and safety features of HNM. If the dose of the HNM increased for manipulating the therapeutic index at a small scale, then there are probably various possibilities in the enhancement of the toxicity.[127] A key feature of HNM discovery and development is the characterization and optimization of their safety and efficacy. These features enhanced the capability to identify an appropriate balanced safety-efficacy profile. The therapeutic index is typically considered as the ratio of the highest novelty with unique exposure in HNM without toxicity. Therefore, to acquire the acquaintance of the HNM utilized for better efficacy is an important parameter and successfully balancing it.[128] There is a need for high stability and that can be achieved only by

encapsulation to get the desired novel formulations. It was reported earlier that various nanoparticles have been developed to date for enhancing the efficacy and effective delivery of HNM. The development of novel HNM is carrying substantial importance and capable of overcoming various constraints (poor bioavailability, in vivo stability, aqueous insolubility, intestinal absorption, and unspecific site of action).[129] A variety of newly developed herbal nanomedicines formulations include the polymeric nanoparticles, nanocapsules, nanoemulsions, transferases, and ethosome, bioactive, plant extracts and food materials have testified. This novel HNM has amazing benefits over conventional formulations derived from the plant extracts for the enhancement of solubility, bioavailability, and expansion of stability sustained delivery, and improved tissue macrophages distribution, protection from toxicity, enhancement of pharmacological activity, and protection from physical and chemical degradation.[130]

IMPROVED PHARMACOKINETIC EFFECT OF HERBAL NANOMEDICINE

The HNM enhance the therapeutic value by reducing the toxicity and side effects of these remedies and simultaneously it also increases bioavailability. In this approach, nanotechnology plays an excessive role in the development of HNM[266-272]. For a long time, the HNM was not well-thought-out for the improvement of novel formulations because of the lack of scientific validation and processing complications. Nevertheless, now researchers are paying attention to phytopharmaceutical research which has the potential to find out the solution for these the scientific needs (determination of pharmacokinetics, mechanism of action, site of action, the accurate dose required) by employing HNM and herbal remedies. For the designing of the novel HNM, there is an urgent need for multifunctional nanomaterials (nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles), , illustrated in figure 6.[131] Because the the, the HNM can consume in a better form with enhanced efficacy. This formulation can be achieved by incorporating them into novel dosage forms with the aforementioned nanomaterials.

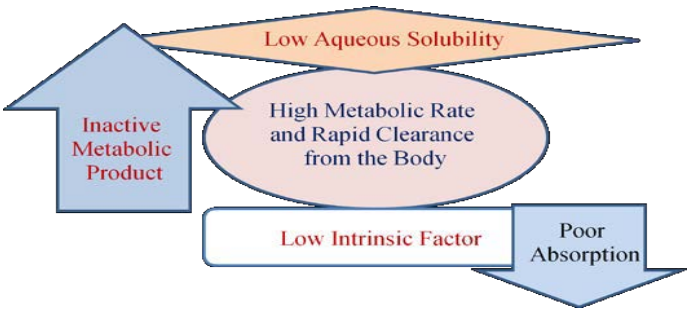

Figure 6. Schematic representation of phenomena that involves many signaling cascades herbal phytomedicine delivery system.

By adopting these novel tactics, the desired novel HNM can be designed. To achieve it, there are the needs of a variety of medicinal plants and herbal extracts containing a lot of varieties of the immunomodulators compounds to full fill the medical needs. Some natural sources (herbal extracts) stimulate the immune system underlined as *Boerhaavia diffuses, Rhododendron spiciferum, Caesalpinia bonducella, Capparis zeylanica, Luffa cylindrical, Withania somnifera and Asparagus racemosus*, etc. Therefore, the impact of nanomaterials in the form of medicine is remarkable. Because of such importance, the nanotechnology is considered as the biggest engineering innovation. Nanotechnology showed the potential to re-engineer the man-made world, molecule by molecule, sparking a wave of novel revolutionary commercial products from technologies in medicine.[132]

DISADVANTAGES OF PHYTOMEDICINE AND HERBAL NANOMEDICINES FORMULATION

While considering their tendency to take up by cells of the reticuloendothelial system and the slow release of the herbal nanomedicine during the liposomes take up by phagocytes are the major drawback of these HNM formulations. These shortcomings must be resolved. Novel HNM is a better option for desired drug delivery that can address the underlined limitations of the traditional delivery systems. Despite these updated novels, HNM cures specific diseases by targeting the diseased site accurately inside a patient's body by transporting the drug molecules.[133] Herbal nanomedicines are not the subject to the same regulations as prescribed for the other remedies. Because of the varieties of the content of the active ingredients may vary among herbal sources and manufacturers, and this potentially may cause a large deviation and variation in the efficacy and safety issues.[134] Plants are the reservoirs of the novel chemical entities and utilized to provide a promising source for the research and development of the HNM for the treatment for the different diseases. Hitherto, being effective, herbal nanomedicines system was escorted by certain unbearable side effects. Photochemical is a revolutionizing field in the area of innovation and development of medicines. As, these chemicals are safer, eco-friendly, low-cost, and less toxic comparatively the conventional treatment methodology. Phytochemicals are selective in their functions and acts specifically on diseased cells without affecting normal cells. All the diseases have complex phenomena comprise of many signaling cascades.[135] Phytochemicals are well-thought-outfit contenders for better formulation of HNM because of their pleiotropic actions on events that occurred at target with multiple manners. The research is in progress for the development of a novel formulation by incorporating the phytochemicals and multifunctional materials. To achieve this goal many phytochemicals and their derivatives are recognized to be considered as potential candidates for the innovation of the HNM. The possibility of contamination and adulteration cannot rule out and thus the herbal ingredient may cause defects in the herbal ingredients and nanomaterials interactions. As emphasized above, people who are using phytomedicine and HNM revealed their feedback to the physicians or pharmacists. These observations altogether exposed the facts in many countries, there are no central bodies for the mandatory reporting as it is there for other orthodox remedies and therapeutic. These are other kinds of hurdle which are creating troubles to proofing the identity of natural formulation. These facts must be included to find out the effectiveness of the occurred interactions within HNM.[136] During

the last few decades HNM has emerged as an effective option to solve the existed problems by tackling them in a better way. As one of the existed problems is that a high percentage of poorly water-soluble HNM existed. There is a need to convert them into soluble form. It is a hurdle for the perfect dose regime. Therefore, by decreasing the size of the multifunctional nanomaterials, it may resolve these existed problems of HNM at nanoscale. These smart changes can significantly alter their physical properties. Modification as required can effectively lay the foundation for a better formulation and open new avenues for their utilization as HNM in a better way. Therefore, various techniques have been considered since these shortcomings are noticed to produce highly water-soluble HNM. These methods mainly resolve the poor solubility issues as well as it's useful for the up-gradation of the proficient and targeted delivery systems derived as HNM. These techniques can be categorized into three main groups which are as follows: top-down, bottom-up, and encapsulation approaches.[137] Among all of them, the top-down approaches have been the primary choice for the industrial preparation of HNM while other methods utilized actively by investigators for exploring futuristic approaches.[125]

CHALLENGES TO HERBAL PHYTOMEDICINE DELIVERY SYSTEM

The discovery of HNM from herbal resources comprises of multidisciplinary features of various themes (botanical, ethnobotanical, phytochemical, and biological techniques) is in demand. Phytochemicals have a lot of characteristics that are capable and suitable for new openings and effective themes be utilized for the innovations in medicinal chemistry and herbal nanomedicine discovery.[138] The impacts of the medicinal chemistry on the various aspects of the chemical synthesis and the pharmaceutical industry up-grade the potential applications of the newly created synthetic analogs with the similarity with the natural products. These efforts can overcome dependency on natural sources. But, the derived herbal components may have low therapeutic potency, low bioavailability, and low metabolism rate. Therefore, there is a need to handle these problems carefully by changing a molecule's structure and converting it into the desired form as per the requirement of the formulation of the noble HNM.[139] These efforts can enhance the possibility for the innovation of the novel strategies to increase the efficacy, potential, and stability of HNM.

A. The High-throughput screening revolution

The current development in metagenomics and screening technologies has explored exponentiation of the volume of useful structural sequence information. These techniques were employed for HNM discovery.[140] Therefore, these methodologies are play an influential role in the innovation of the HNM from phytochemicals. These developments in the new manufacturing paradigm are very useful expressively and are necessary for fast-track development of HNM. By remodeling the theme of HNM manufacturing, it is quite possible to develop the desired remedy. Here, the authors outlined these developments and concerned outlook by integrating next-generation technologies, metagenomics, and metabolic engineering. The key idea is to incorporate these modern approaches with traditional methodologies for discovering, manufacturing, and development of NHM.[141] These techniques deliver better-quality patient compliance with the sustained release for a perfect targeted action by delivering herbal extracts through HNM. This assessment recaps the evidence of many novel techniques used for taming safety and efficacy in the implementation of HNM in a practical scenario. The existed active ingredients of herbal extracts and their respective potential biological activities influence the formulation of the novel HNM and concerned therapeutic response. The high molecular screening technology recently developed as CometChip technology, which is capable of empowered the evaluation of different pathways and components (single-stranded DNA breaks, basic sites, and alkali-sensitive sites in cells) and widely used in the development of HNM. Combinatorial chemistry and high-throughput screening (HTS) techniques are the tools utilized for HNM discovery.[142] The chemical or cellular assays swiftly recognize whether the small molecules bind to a specific biological target or not. Recently, these methodologies and techniques were employed for the analysis of the potential medicinal molecules by rapid screening. These drug molecules have the potential as a better therapeutics. Combinatorial chemistry-based strategies[143] also frolicked a vital role in the development of noble HNM.[144]

B. Natural product renaissance

An eccentric approach of HNM discovery embraced[145] by the implementation of the combinatorial chemistry to find out the diversified synthesis routes for the concerned manufacturing. These methodologies deal to access a pre-selected range of fairly structured diverse drug molecules for providing large drug/medicinal components required in the formulation of the novel HNM in a short period.[146] These high-throughput biological assays are conceivable enough to be employed in the advancement of biotechnology. These problems will start whenever there is no option available in the list of natural products to be considered as drug/medicinal molecules. In absence of it, the synthesized drug formulations may utilized, but as they displayed undesired side effects. Therefore, the herbal extracts are better, because the utilized herbal components will not display any specific binding features required for novel drug molecules. The natural products owning extraordinary and potency specific drug qualities must be preferred over the chemically designed drug molecules. These aspects must be answered scientifically. This evolutionary approach authenticated nature's high-throughput synthesis and screening potential that make it efficient as biologically active compounds.[147] Natural products are well-defined topologies that embellished with functional groups (providing hydrogen bond acceptor/donors) requirements for effective functioning by the orientation. The natural products are capable of binding biological targets (protein binding sites) often interfaced with the different proteins having numerous structural sequences. The mode of action of the secondary metabolites[14] started by generating organism, yet equally potent, and may affect targeted locations.[148] The availability of the herbal extracts provide a better option comparatively others, so it must be considered in tailoring HNM having high therapeutic index (better bioactivity, high

pharmacokinetics, and solubility) as naturally occurring molecules have.[145]

C. Fragment-based screening and technological advances

Advances in analytical technology and alternative assay strategies are crucial in the development and discovery of a novel formulation of HNM for a more viable treatment option. Perfections in the analytical sensitivity and precision of assay revealing techniques can do a perfect post-mortem of the nanomaterials and herbal extract interface. These advances in the enabled, and fragment-based screening approaches[149] play an important role in these discoveries. Advances in computing systems are also assisting to convert these HNM formulations into faster and more effective therapies. Today, drug binding sites can routinely model to find out the possibilities of the action of phytomedicines or herbal extracts. Therefore, it is quite easily detectable to understand how these drugs/medicines molecule can occupy the space necessary for proper action at the diseased sites. By adopting these means, it is easy to forecast the action mechanism of the HNM[150] by underlining the preferred routes of the functional groups of the larger phytochemicals during their interface with binding pockets of nanomaterials. It, further, analyzes how the phytochemicals structures can alter to fit binding/target locations. Computational[151] analysis was utilized for the prediction of the target outfits. The same is feasible and applicable now. The identification of the needs of the potential targets for the prediction of off-target effects of the nanomaterials and herbal extract formulation must be underlined. During the combination of the high-throughput phenotypic screening strategies, the main objective is where a specific target is located. These methods displayed potential to be utilized in the further analysis. Once desired drug molecules are identified in the herbal extracts, the latest herbal nanomedical delivery strategies must employ for its preparation.[152] Current improvements in HNM sequencing have ensured identification of many metabolic pathways exploit for it.[153] These approaches based on altered intermediate pathways existed within HNM to carry out complex chemical modifications in naturally occurring drugs/medicine molecules for the intensive formulation.[154]

D. Diversion of resources to combinatorial chemistry

By using the combinatorial tools probably to build up an analysis pattern of HNM, it is possible to restructure the basic needs as required for the routinely fashionable practices. These trials are efficiently used to make new leads in the swiftly emerging therapeutic innovation by adopting the aforementioned combinatorial approaches. At present, it is employed to craft drug molecules and is very helpful in the development of the laboratories to screen these novel bioactivity herbal components. This new intense innovation is underway to discover new HNM rapidly. These efforts are spared enormous outlays in the preclinical improvement by changing the vital means during HNM analysis. It can be achieved by approaching[155] structural modification of natural products in several ways. The first and the most possible way (although least diverse) is to do chemical alterations. These modifications have been done by doing functional-group transformations as natural products have. These semisynthetic approaches have helped in providing analogs rapid, but it is fairly inadequate in terms of variety.[156] Another leeway is to use structural engineering to reconstruct the biosynthetic pathways (combinatorial biosynthesis) leading in the development of the medicines similarly as natural remedies. It also precincts concerning modification to the extent of diversity. Arguably, for the preparation of HNM, the most versatile approach is the design of a synthetic path for the synthesis of a specified phytochemical compound. It permits to outline of the deep-seated structural distinctions routes for the synthesis of the targeted HNM. This approach may be defined as the total synthesis route.[157] The variances between three different compound classes (natural products, molecules from combinatorial synthesis, and herbal nanomedicine molecules) explored in this methodology. The major structural differences between natural and combinatorial compounds originate mainly from those properties. These strategies were introduced to make combinatorial synthesis more efficient.[158] The main components are mainly comprised of aromatic rings, introducing complex ring systems, the degree of the saturation of the molecule, the number, and ratios of different heteroatoms. The herbal nanomedical molecules originate from both natural and synthetic sources, thus they cover a joint area in the property space of nature as combinatorial compounds. We put it forward by mimicking the firm distribution properties of phytochemicals. It might make combinatorial products substantially more diverse and have greater biomedical relevance.[159]

E. Technical difficulties

The variations presented in the source material, the difficulties of isolating the active constituents, and the costs of collection are the major concerns. The main components are phenol and flavonoids that existed in the herbal extract. These components are full fill antioxidant deeds and perform a role in the development of HNM to cure an age-related disease caused by oxidative stress. The required alteration was done in the beneficial phytomedicines that existed in the herbal plants to achieve novel HNM for the pharmaceutical needs. Therefore, going on research on herbal remedies is particularly noteworthy to updates research on conventional HNM. The analysis of HNM twitches with requites pre-extraction and extraction procedures that are a vital step for processing bioactive constituents existed in herbs.[160]

F. Phytochemicals or bioactive compounds as herbal nanomedical agents

The plant contains many compounds commonly known as phytochemicals. These were identified as bioactive compounds, and can display antimicrobial activity. These phytochemicals have already effortlessly been tested and used in humans for the treatment of the microbial infection. Therefore, such herbal remedies containing these components are very much effective as medicines to increase the life span of comparative antibiotics. These herbal remedies are extracted from the plant sources and effective to full fill the needs.[161] There are several possibilities of misappropriation in the utilization of these traditional antibiotics. Many other complications also existed in the prescription to make it a more complicated option as it was not utilized in a better way.[162] Phytochemical displayed antibacterial effectiveness because of these components and different chemicals (phenolics,

terpenoids, and other essential oil constituents, alkaloids, lectins, and polyacetylenes). The major subclasses of their constituents are phenols and phenolic acids, quinones, flavones, flavonols, tannins, coumarins, terpenoids, and essential oils, alkaloids, lectins, and glycosides. For instance, Emblica Officinalis, saracaindica, and Terminalia arjuna[163] showed antimicrobial activity and capable of resisting pathogens similar to the other phytochemicals.[164,165] These phytochemicals inhibited bacterial growth by various mechanisms as similar as antibiotics do. This HNM resist pathogens and unveil a plethora of antibiotic-resistant mechanisms to attack to nullify antibiotic actions. Their antimicrobial properties do enzymatic alterations and also the upgraded antimicrobial effectiveness may be achieved by the modification and overproduction of abridged herbal nanomedicine. The HNM uptake initiates metabolic activities and bypasses targeted pathway for extracellular active pumping of HNM subsequently by protein binding. The achieved results displayed and summarized[167] in Table 1 and some of the studies showed exploratory outcomes.[134] Some of the phytochemicals were considered as the potential antimicrobial agents as per mechanism and action.[168] These studies have revealed that the action of phytochemicals on the bacterial cell, or the targeted site, were observed, detected, and reported. The allicin (diallyl thiosulfinate), a phytochemical usually assimilated from Allium sativum (garlic), has potent antimicrobial activity and inhibits RNA synthesis and capable of intracellular interaction with thiols and thiol-containing proteins.[159] Plant alkaloids, including berberine, and piperine, found in Berberis species and Piper species, can interact with the bacterial cytoplasmic membrane, intercalate with DNA, and inhibit efflux pumps in S. aureus. Similarly, reserpine inhibits efflux pump.[169] Epicatechin gallate and epigallocatechin gallate, constituents of two major flavonoids found in green tea, inhibits antibiotic efflux pumps in methicillin-resistant S. aureus (MRSA) and E. coli. Gallic acid, tannin inhibits permeability of the outer membrane in Salmonella spp. Quercetin, a component of propolis, binds to the GyrB subunit of E. coli DNA gyrase and inhibits the enzyme's ATPase activity. Studies are limited as of complex mechanisms, but it is clear from the different studies that phytochemicals have potential to combat the problem persisted in the development of effective antimicrobial resistance. These formulations can act on multiple biochemical targets of the bacterial cell, but, the problem arises in very initial stages when the affordable synthetic HNM cannot be achieved in combinatorial libraries. These researches, and outputs, enhanced possibility to find out an herbal extract in which spectacles potent biological activity components existed. The main troubles are, some of them have poor water solubility or very short circulating life and face noteworthy development trials.[170] Despite these challenges, much natural herbal medicine such as the artemisinin, curcumin, triptolide, and capsaicin have been extensively studied and recommended for the clinical trials. The number of capable compounds stumbles in irrelevance. Not only in the natural herbal nanomedicine selection and isolation, but the delivery of natural herbal nanomedicine utilizing conventional dosage forms is also puzzling. The main efforts require to solve problems persisted in the delivery of HNM which are as follows: (i) Varying structures of the compounds, (ii) Aqueous solubility, (iii) Low bioavailability, (iv) Poor permeability(v) Instability in biological milieu, (vi) Fast oxidation under basic conditions and, (vii) Rapidly passing clearance and metabolism before reaching to systemic circulation. All these challenges intensify the problem of paucity of new antimicrobial agents.[171]

RECENT DEVELOPMENTS IN HERBAL, PHYTOMEDICINE, AND FORMULATION AVAILABLE

Nanoscale multifunctional materials can enrich the biological activity theoretically and practically for growing the possibilities required to overcome complications allied to HNM.[172] However, significant trials undergo for the development of clinically feasible therapies. Trials conducted to detect the interface of the biological systems and signify for the fundamental practices for decoding HNM in therapies. A lot of the new challenges persist in the development of HNM. For example, formulations derived from nanotechnology must be employed for the engineered HNM. This is the main theme requirement for the development of effective remedies. But, it is the foremost challenge. These HNM formulations can display biological effectiveness aforementioned. The outputs are supported by the use of the nanoparticle in the formulation of the herbal remedies to treat the diseased cells/ organs. The outputs are recognized and appreciated by the physician rapidly. These formulations have high grades of biologically effective components. Therefore, the required feasibilities to scale-up these experiments are capable to fetch groundbreaking therapeutic as per the needs and it can be achieved by the prompt efforts. The flexibility in the methodologies utilized for the findings required multifunctional outlines. These efforts can fulfill reasonably a lot of biological and therapeutic necessities. Nearly non-essential newfangled encounters can disturb efficiency of HNM. There is a need of such efforts that can nourish ethics to stop toxicology and enhance biocompatibility.[173] Nanotechnology is the groundbreaking emerging themes and HNM is considered as an outcome of it. The Herbal-nano interface has possessions of a self-steering accessory as an explicit ligand, therefore, the nanoparticles can be utilized for targeting. These multifunctional materials have exceptionally small size and are very much effective in the infected pathological areas.[174] HNM is a novel tactic to amaze downsides of traditional herbal delivery systems.[175] By exploring the relationship[176] between nanotechnology and herbal remedies, the feasibility of such formulations were detected. Therefore, it can convey the compliance of nanotechnological methodologies for bioavailability enrichment of NHM. Interestingly, the pharmaceutical understandings used nanoscale materials to diminish toxicity and side effects of HNM, if any.[177] The awareness for the investigation of the magnetic nanocapsules has been augmented significantly. The intermediate circumstances existed between mass and atomic materials favored formation.[178] These nanomaterials may alter magnetic behaviors as required by their analogous counterparts.[179]

Table 1 : Summary of various nanostructuredherbal formulations (herbal nanomedicies drug delivery system)

Formulations	Active ingredients	Biological activity	Method of preparation	Applications of the formulations
Diclofenacdiethylamine and curcuminnanocarrier transdermal gel	Curcumin	Anti-inflammatory activity	Encapsulation with sonication	Enriched biological activity Targeted effect
Nanotransfersomes of diclofenac diethylamine and curcumin	Curcumin	Anti-inflammatory activity	Encapsulation with sonication	High bioavailability Enhanced permeation C
Electrospun gelatin nanofibres containing Centella asiatica extract	Alcoholic, phenolic compounds carboxylic acids	Anticytotoxicity and antibacterial activity	Electrospinning	Promising and potential material for use as wound dressing materials
Polycaprolactone/polyvinyl pyrrolidone nanofiber mat with bark extract of Tecomella undulate	Alcoholic, phenolic compounds carboxylic acids	Antibacterial activity	Nanofiber fabrication through electro spinning	Great potential in drug delivery, wound healing and treating against surface pathogenc microorganvesms
Oleanolic acid loaded PEGylated PLA and PLGA NPs	Oleanolic acid	Anti-cytotoxicity against cancer cells	Ring opening polymerization followed the by nanoprecipitation method	High potentials to develop into an effective anticancer delivery platform for cancer chemotherapy
Incorporation of four prenylated flavanones from leaves of Eysenhardtia platycarpa	5,7-Dihydroxy-6- methyl-8-prenylflavanone; 5,7- dihydroxy-6-methyl-8- prenyl-4_-methoxyflavanone; 5,7- dihydroxy-6-prenylflavanone; asnd 5-hydroxy-7- t	Anti-inflammation activity	Oil, solvent anfactant cosurfactant mixture	Ac potential topical antiinflammatory agent
MUDDS with four units	Realgar, frankincense and myrrh oil, musk, and bezoar	Antitumor activity	Ball milling followed by solvent evaporation	High antitumor activity High bioavailability
SNEDDS formulation of Zedoary turmeric oil	Essential oil	Oral bioavailability	Self nanoemulsion	Increase drug loading Decrease the inert oil requirement
SNEDDS formulation of quercetin	Quercetin	Anti-liver toxicity Self nanoemulsion	Protective effect against paracetamol induced hepatotoxicity	Enhance the activity of antioxidant
SNEDDS formulation of Persimmon (Diospyros kaki) leaf extract	Flavonoids (Quercetin and Kaempferol)	Antioxidant activity Self nanoemulsion	Self nanoemulsion	Promising method for poorly aqueous soluble drugs including the extract of herbal medicine to achieve a significant improvement in bioavailability
Witepsol SLNPs and Carnauba SLNPs	Thujone, pinene, camphor	Antioxidant activity	Hot melt ultrasonication	Suitable vehicle for herbal extracts with high stability during digestion A significant release percentage of phenolic compounds at the small intestine
Polymeric NP formulation of Syzygium cumini	Gallic, chlorogenic caffeind ellagic acids, catechin, epicatechin quarcetin etc	Antifungal activity	Emulsification/evaporative solvent technique	Significant attenuation against the chronic complications of diabetes mellitu

Continied…Table 1 : Summary of various nanostructured herbal formulations (herbal nanomedicies drug delivery system)

Formulations	Active ingredients	Biological activity	Method of preparation	Applications of the formulations
Curcumin and temozolomide loaded magnetic NPs	Curcumin and temozolomide	Anticancer and antitumor activity	Nanosuspension with sonication	Dual drug delivery system (Cur + Temo) is provoking greater anticancer activity by stimulating cell death pathways
NiNPs of Aegle marmelos correa	Amines, amides, phenolic and alcoholic	Anti-inflammatory and mosquito larvicidal activity	Nanosuspension	Excellent antiinflammatory agent Acts as a drug carrier for the control of Cx. Quinquefasciatas
AuNPs of Pistacia integerrima gall extract	Amines, amides, phenolic and alcoholic	Antifungal activity	Nanosuspension	Significant attenuation of pain and muscle relaxant effect
Fluorescent AgNPs of Artemisia annua	Amides and phenolics	Anticytotoxicity and antibacterial activity	Nanosuspension	Fluorescent properties can be exploited in biomedical applications Biocompatible cytotoxicity against human erythrocytes
AgNPs of Bauhinia tomentosa Linn	Amines, carboxylic acids, aldehydes and ketone	Anticancer and antioxidant activity	Nanosuspension	Potential agent for cancer therapy
AgNPs of Mukia scabrella	Cysteine residues in protein	Anti-microbial activity	Nanosuspension	Antibacterial activity against MDR-GNB nosocomial pathogens
Curcumin loaded NPs of HPMC and PVP	Curcumin	Anti-malarial activity	Solvent emulsion – evaporation technique	Beneficial for the prolonged utilization of the formulation as an adjuvant anti-malarial therapy to prevent the recrudescence and reduce the dose of the standard anti-malarial drugs
Curcumin-lipid NPs with Gelucire 39/01, Gelucire 50/13, percirol, compritol and polozamer 407	Curcumin	Anti-microbiological activity	Hot homogenization	Promising alternative for the manipulation of curcumin to overcome the clinical applications
pH sensitive	NPs loaded curcumincelecoxib combination	Curcumin Anti-inflammatory and antioxidant activity	Solvent emulsion evaporation	Enhanced efficacy for mitigating ulcerative colitis
Solid lipid nanoparticle herbal formulations	Cryptotanshinone is the major active ingredient from the roots of Salvia miltiorrhiza Bunge	Anti-in-mmatory, cytotoxic,anti-bacterial, anti-parasitic, anti-angiogenic	Cryptotanshinone	Enhancement of bioavailability of cryptotanshinone
Solid lipid nanoparticle herbal formulations	Cryptotanshinone is the major active ingredient from the roots of Salvia miltiorrhiza Bunge	Anti-infammatory, cytotoxic,anti-bacterial, anti-parasitic, anti-angiogenic	Curcuminoi-ds	Enhanced stability of curcuminoids

Sometimes, the HNM discovery faced worry in promotion because of their vicious side effects.[180] The herbal remedies are positioned inside nanocapsule for transportation directly to target site without any toxicity.[118,171] These nanoscale tools showed a greater ability and extraordinary therapeutic potential in their performances.[181] The creation of nanocapsules is a central idea of new theme and can be utilized in pharmaceutical, biochemical, electrical, optical, and magnetic research. Their main requirement is high transportation rate of bioactive molecules which is necessary to treat disease. These features matched with the current need. There are plentiful challenges existed in the adopted mythologies employed for the improvement of transportation. There are very small chances for a successful experiment performed for enhancement of drug transportation necessary for better-quality therapy.[182] Cuscuta Chinensis is a commonly[183] used in traditional Chinese medicine and recommended to nourish the cells of the liver and kidney. It contains flavonoids and lignans, which are miserable water-soluble. The absorption of these components could be inadequate during oral administration. It was notified that nanoparticles[184-185] have an amazing water-soluble properties required for a good medications. Therefore, it will affect treatment prescription. Artemisinin nanocapsules are

condensed as artemisinin crystals incorporated into chitosan, gelatin, and alginate for the perseverance of controlled discharge. It helped in up-gradation of hydrophilicity of nanocrystals during encapsulation. The properties of polyelectrolyte solutions delimited the rate of the herbal nanomedicine release in the form of various components (polyelectrolyte type, number of polyelectrolyte multilayers, sodium chloride concentration, and ethanol concentration in polyelectrolyte solution).[186] The other phenomena can be employed for the number of polyelectrolyte multilayer, and sodium chloride concentration to ethanol concentration in polyelectrolyte solution.[186] Anti-Trypanosomal, chagas disease is a neglected parasitic disease caused by protozoan Trypanosoma cruzi. New antitrypanosomal preferences are looked-for to thwart hitches, comprising a high rate of cardiomyopathy.[187,188] A natural substance, lychnopholide, has revealed therapeutic potential, especially when encapsulated in biodegradable polymeric nanocapsules. Echocardiography revealed concentric left ventricular hypertrophy with well-kept-up ejection fraction, diastolic dysfunction, and chamber dilatation at end-stage. Single cardiomyocytes are accessible to rehabilitate contractility and Ca^{2+} handling, with spontaneous Ca^{2+} waves in diastole. Extraordinarily, the encapsulation of lychnopholide prohibited cardiac alterations that were encouraged in vivo by free form recurrent prescriptions.[189] Nanocapsules had no adverse cardiac effects. Overall, it was found that the lychnopholide is accessible in the nanocapsules form for more decisively performance as HNM to cure Chagas disease with minimal cytotoxicity.[190] Berberine-loaded targeted nanoparticles that are an isoquinoline alkaloid and extract from the bark and roots of the Berberis vulgaris plant. It has been used in Ayurveda medicinal as it holds antimicrobial, antidiabetic, anticancer, and antioxidant properties. But the poor solubility of berberine leads to poor firmness and bioavailability in medicines that decrease the effectiveness.[24,191] Hence nanoformulations of berberine have significance in eliminating the preventive issues of alkaloids by improving the consumption in pharmaceutical manufacturing. Sodium alginate polymer was used to summarize berberine within nanoparticles by emulsion solvent evaporation method by using it as a surfactant. The berberine loaded polymeric nanoparticles revealed better antibacterial activity paralleled to an aqueous solution of berberine by well diffusion assay. To develop fucose-conjugated nanoparticles as a regulator to release of berberine[192] that validate the existence of the particles into contact[193] with Helicobacter pylori and boost the explosive outcome of berberine on H. pylori[194] growth.[28] Fucosechitosan/heparin nanoparticle-encapsulated berberine was prepared[195] and confocal laser scanning microscopy was employed to supervise the carrying proficiency. In vivo study, the berberine-loaded fucose-conjugated nanoparticles revealed an H. pylori clearance effect. These outcomes point out that berberine-loaded fucose-conjugated nanoparticles expert an H. pylori stipend result that shrinks gastric inflammation in an H. pylori-infected animal study. The natural product berberine (BBR), existing in several plants, stirs significant benefits because it contains many pharmacological properties. Though, the auxiliary expansion and claim of BBR had been fraught by its meager oral bioavailability. In this toil, the polymer-lipid hybrid nanoparticles (PEG-lipid-PLGA NPs)[196] loaded with BBR phospholipid complex using a solvent evaporation method employed for refining oral BBR efficiency.[197] The BBR-soybean phosphatidylcholine complex (BBR-SPC) could enhance the liposolubility of BBR and improve the affinity with the biodegradable polymer to increase the herbal nanomedicine-loading capacity and controlled/sustained release.[198] It is evident that it is the foremost object and by using polymer material for real encapsulation of BBR, the enhanced bioavailability may be achieved.[133] Breast cream, “nanotechnology and the ageless Thai herb, Pereira mirifica” and that niosome “expands the cellular substructure and improvement of the lobules and alveoli of the breasts,” with increased size from one to three cups.[134]

Herbal nanoformulation was utilized for hair care too. Some of them are nanoceuticals citrus mint shampoo, and conditioner having nanoclusters that provide a healthy shine to hair. There is one more product that is a shampoo with an herbal blend and contains any one of them, nettle leaf extract, black elderberry extract, chamomile combined with citrus and mint oils. These herbal products are employed and utilized to nourish hair.[199] These shampoos are very useful in fortifying the hair follicles, repair scalp circulation, benefit weakens inflammation, stop dandruff, boosts hair volume, and generate shine. Pearl powder, an herbal remedy, is used to enhance skin beauty[200,] and this product is underlined as a supreme beauty refresher. It was evident that the pearl powder can stop foiling responsible for the growth of melanin. It removed surroundings black spots and dark layers of the skin. These products are ordinarily applied to stop aging impacts. The components of it can block the skin flattering responsible for the old looking, wrinkled, and sagging looks. These remedies contain nutrition and enclosed dozens of minerals, including calcium, magnesium, zinc, iron, strontium, copper, selenium, silicon, titanium, and more. Pearl, a beauty remedy, contains calcium carbonate, magnesium carbonate, calcium phosphate, ferric oxide, and silica. Besides, it has dozens of minerals. Pearl also comprises many amino acids that are essential for health.[201] Many constituents of the pearl participate in DNA and RNA metabolic activities and, therefore, these components are capable of cell renewal. It has been revealed that mucopolysaccharides presented in the composition of the pearl showed the potential to reduce the wrinkles. These herbal remedies can increase libido and sexual potency in humans whenever it decreased because of aging. Pearl powder is a nano-sized powder and naturally occurring components. It occurred in 100% finely ground freshwater and extracted to form pearl powder. This herbal remedy, pearl, harvested in Zhejiang province, the largest origin place of freshwater pearl in China. Several modifications have been done that verified their applicability and to enhance their potential as an herbal reagent. It further suggested that the best way to use pearl is to utilize it as fresh. But, using the whole pearl powder may be problematic because some of its physical properties are not considered suitable. Further, it showed a high bioavailable character. Recent signs of progress in the field of herbal remedies and grinding technology initiate new hopes to use it in a better way. These

technologies inbuilt some features that allowed to grind the pearl into a powder at the nanoscale. This powder is easily and entirely absorbed by the body and fully applied once it is in the bloodstream. Lipo nano glutathione, many orally disbursed nutrients, but these remedies have a poor absorption rate. These nutrients are incorporated into a liposomal delivery system that can absorb it substantially at a higher rate. Glutathione, an antioxidant secreted by the body to get rid of toxins. It is an essential need that benefits the body. It removed the toxic metabolic waste from the body and also enhance the immune system.[202] These remedies decrease oxidative stress, inflammation, the levels of the toxic chemicals, and aging impacts. The oral intake of the glutathione is not effective because of its poor absorption. Therefore, the intravenous dose of the glutathione is very effective. It cannot be used as an inhalation as it contains nebulized glutathione. Thus, the glutathione is incorporated in nanomaterials that are performed as a liposomal delivery system. The new formulation of the glutathione has similarities with the blood compositions that are infused as per the need. Nano-liposomes is the creation and a new formulation employed for transportation of the glutathione.[203] To pass over the gut safely, there is a need for the coating before these remedies were processed as nano/micro particles in the form of fat-soluble nano/microbubbles to offer protection. These bubbles are portable devices that can go through the bloodstream and reach certain cells of the body for the proper action. Nano-bio interface is the natural enhancers and incorporated in different kinds of materials such as grass, cereals, pulses, flowering, and fruiting plants. The nano-bio interaction enhanced growth. Other outcomes of it are applicable in many assistances. These remedies enhanced the uptake and assimilation of trace mineral rapidly to spot-on minor micronutrient deficiencies. These nanoscale formulations enhanced water absorption and other nutrients[204] from the soil in plants. These remedies act as comprising chelates agents and displayed significant nitrogen sparing effect. These tactics saved energy significantly in the plants. These formulations further performed as divergent agents to succeed chelation as per the composition of the soil, maintain water holding capacity, and CEC levels. These HNM remedies promote the enlargement of roots required for the better propagation of rootlets.[205] Overall, these efforts assist enrichment for the synthesis of enzymes and the enhanced photosynthesis.

These remedies can also enhance plant productivities by increasing the production of the vegetables, flowers, fruits, improve the quality of the fruit, and enhance the flower brightness of the colors. These formulations may apply to increase the post-harvest storage life of vegetables and fruit. These natural remedies can improve passivity importance by increasing the resistance potential of the plants necessarily required to kill the pests. These efforts increased the yield by 15 to 20%. These components are very easily applied and anyone can handle them because all of these formulations are nontoxic. Therefore, these natural remedies are user friendly and not induce any harm to the environment.[205]

Canssu-5 nano naturalis is one of the herbal remedies applied as angiogenesis inhibitors. This herbal formulation is utilized in the development and production of health care products as a natural supplement. This remedy was obtained from the standardized extract of the Orthosiphon aristatus and Orthosiphon stamineus herb. The herbal components that existed in it have strong anti-inflammatory and anti-angiogenic activity.[206] These herbal extracts were used in the formation of the HNM that were achieved through nanoformulation. These technological approaches are utilized to assist the absorption phenomenon of the phytochemicals in detecting the lower absorbance capacity. The herbal-nano formulation contained rosmarinic acid, which is a powerful natural antioxidant and displayed anti-inflammatory properties. The canssu-5 nano is approved by the validation technique by approving the product of anti-angiogenic activity. These reassurances poise product superiority. The features of HNM are enhanced by incorporating the magnesium in it. The obtained formulation contains magnesium performed as wonder HNM. There is no proper scientific report available in the support of such claims, but the clinician pleased and appreciate it. The assistances initiated by the use of HNM proved that these remedies are enhancing the muscle strength and improve the nerves, regulates blood sugar levels, promotes normal blood pressure, and reduce the risk of heart attacks. The rare scientific pieces of evidence proved the importance of these remedies in the regulation of diabetes. Several health reports were published concerning findings derived from the use of several herbal remedies. For example, the species of the bitter melon contains glucose-lowering components such as polypeptides and glycosides.[207] Dietary supplementation of Fenugreek is employed to cure pre diabetes symptoms because it is capable to decrease insulin resistance. Another example is Gymnema extract, other herbal remedies used in the prevention of blood sugar. Gymnema leaf extract is recommended for diabetic patients. It evidenced that within 90 days of the period, the continuing use of the extracts of it lowers blood sugar levels. It is also implemented in the treatment of the people suffering from type 2 diabetes. Therefore, it is clear from the pieces of evidence that Gymnema leaf or extracts reduce diabetic problems, while it was used as a long term perspective. The mixture of the vitamin D3, natural turmeric, curcumin, and multifunctional nanomaterials showed strong anti-inflammatory properties. This remedy is also applied as a pain reliever. The formulation of the AEGIS-herbal nanotechnology is employed for the prevention of bacterial aegis.[208] The herbal nanotechnology-based therapeutics also suggested for the treatment of bacterial infestation. The serum derived from the formulation of the abhaibhubejhr rice and nanoscale materials strengthen hair roots and decrease hair fall. The Tag Nano NPK, the nano-fertilizer granules, are the best remedies and a groundbreaking option for enhancing the production of the crops. This formulation is the first of its kind product derived by the combination of the gluconate fertilizers and accessible nano nutrients. Tag nano NPK is an inimitable protein-Lacto-gluconate formulation, prepared from the mixture of the organic compounds, chelated micro-nutrients, vitamins, probiotics, seaweed extracts, humic acid, nitrogen, phosphorus, and potash. This nano-herbal fertilizer enhanced the overall growth and yield of the crops. These herbal remedies are highly capable to enhance the rate of photosynthesis by reducing the intensity of chlorosis. Their

compatibility is greater with the crops compared to the chemical pesticides and fertilizers and thus these remedies significantly reduce the dependence on chemicals. These herbal remedies are eco-friendly with no side effects. The turmeric-nano is a new formulation based on herbal nanoformulation. The development-related strategies are in the pipeline to launch shortly.

TOXICITY ISSUES OF HERBAL NANOMEDICINES

Although HNM may promise endless opportunities and applications that can be utilized in the treatment of various diseases, during their utilization the safety issue cannot overlook. Because few of them may be toxic. The changes occurred in the physicochemical and structural properties of herbal remedies after the interface with nanomaterials. These interactions within the composition may lead to some toxicological impacts.[209] These mixtures of nanoscale having low molecular weight polymer molecules and the herbal remedies contain bio-macromolecules are the best composition for the development of more efficient HNM. These green nanotechnology methods are highly capable in creating novel HNM formulation. The perfections of these green processes have led towards the formation of low toxicity remedies having high biocompatibility. In these formulations, the main aim is to use biomaterials containing proteins and lipids. The applicant of green nanotechnology has helped to escape one of the biggest complications existed in HNM formulations. However, the research frazzled here is flawless. These noble efforts are architecting non-toxic and operative nanoparticles to be utilized in these formulations.[210] The persistence of nanomaterials in the body may disturb other biological features, therefore, there is an urgent need to design strategies that could extract these nanoparticles from the body after the treatment. These strategies must have a better clearance scheme for flushing out of these nanoparticles. These methodologies are quite helpful to avoid unnecessary side effects initiated because of retention of these nanoparticles. One of the fears concerning the toxicity of these nanoscale devices in-vitro/in-vivo is to design a toxicological evaluation model and that must be the priority. Nanotechnology-on-a-chip[43] is another dimension of lab-on-a-chip technology, these enabled features may further expose first-order kinetics of these HNM.[211] There are a few possibilities, if these technologies were not implemented sensibly, and then these innovations may hinder the development processes. The possibilities of the deterioration in HNM efficacy cannot be overruled and their formulation may decompose before the target. Thus, any defects may cause complications in their efficacy, as it can be concentrated. Keeping it in mind, many efforts are done to achieve enhanced traditional oral delivery systems by employing nanoengineered systems. On the other side, these herbal nanoformulations enriched bioavailability. There are several inhibiting factors (racial diversity, host-defense variability, and genetic shift, and drift to assertion safety and efficacy of HNM which may further analyze to achieve the goal.

FUTURE PERSPECTIVE OF HERBAL NANOMEDICINES

The development of several formulations of HNM in the phase of the clinical trials. As per the need, the only necessity is to develop a remedy that has a better therapeutic effect. These remedies must have a better drug delivery strategy that can be successful to perform at the affected sites accurately. The impact of these remedies must be effective in the entire body and there must be no compromise as existing in the current therapies. There are so many strategies that are implemented to reduce side effects, toxicity, and hypersensitive impacts[212] but also these HNM will increase the patient's immune power as such that is the much more desirable aspect. The perception of HNM is wonderful and may be applied for the treatment of various diseases. Therefore, few potential research groups are developing these remedies and providing attention-grabbing results. Hence, the herbal remedies incorporated in nanocarriers will increase their potential and these formulations may be capable to treat various chronic diseases. Defiantly, these HNM will boost human health.[213] Many successful efforts have been made and evidenced by the impact of the nanomaterials as a component of HNM responsible to enhance therapeutic indexes. These HNM formulations are successful just because of flourishing components that were available as medicinal compounds containing antioxidants. The other constituents of these remedies can increase the possibilities to cure a disease. [214] These collaborative efforts were implemented to improve the impact of traditional herbal by transforming them into HNM. The other aspect of nanotechnology is that it emerged as attractive therapies in pharmaceuticals to sort out health issues. It is expected that the effectual and valuable relevance of herbal remedies increased interaction with nanocarriers and that is significant in the formation of HNM.[215] There are several types of applications of nanotechnology in formulation procedure of HNM which are as follows: (i) nanomaterials may perform as a carrier and able to transport the active substances and the remedies employed for accurate diagnosis, (ii) capable to repair the genetic material and perform cell cleaning, (iii) can improve the natural physiological functions and (iv) utilized for in-vivo procedures for imaging for the 3D view to differentiate them more easily.[129,216] The genes, nucleic acids, proteins, molecules, and cellular processes can quite visible in presence of quantum dots. There are some nanoparticles in the form of semiconductor crystals that can diversely change electronic and optical properties.[217] Because of the enormous stability and brightness, these photo probes displayed a luminosity that is 1000 times greater than conventional contrast media. By employing optimized nanoimaging methods, it is quite possible to detect the position, and size of tumors more accurately. These methods are more efficient competitively to conventional methods. Therefore, the implementation of nanotechnology is prevailing for the development of alternative medicines, methods for controlling and curing diseases. Research and development are centered on this 100-year-old concept for transportation of the active substances at the targeted. For the realization of it, this is looking imaginable for the first time by applying nanotechnology.[218] The biologically synthesized nanoparticles showed better chemotherapeutic effects against few microbial diseases. By implementing the

nanotechnology, it looks quite possible to achieve the set targets that were in high demand. This HNM is quite effective in malaria treatment and cancer chemotherapy. The use of nanotechnology allowed researchers to innovate new HNM formulation that can enter into cancer cells without damaging the healthy cells. Recent advances in the development of HNM transformed them into a piece of anti-cancer agent. These evidences proved that these modifications defiantly enhance the efficiency of the nano-sized dosages of camptothecin-derived as HNM. These HNM formulations target DNA topoisomerase in cancer therapy.[219]

Recently, nanotechnology has drafted plant viruses for HNM delivery to treat cancer. The use of HNM increased because of their enhanced abilities that can be employed to treat different diseases by not displaying any side effects. The development of a novel HNM has considerable importance, which can overcome various limitations by improving certain factors. The various factors of HNM such as bioavailability, in vivo stability, aqueous insolubility, intestinal absorption, and unspecific site of action are few factors that can be improved by applying these aforementioned parameters and techniques. It is quite interesting that nanoscience enriched HNM efficacy for treating chronic diseases (cancer and pain).[120] The vision of the HNM is the vision of the future and these HNM can treat the patients by dosing tailor-made therapeutic at the molecular level. These remedies are quite effective to treat those diseases which are in the development stage. The polymer nanoparticle, magnetic nanoparticle, and metallic nanoparticle are the main featured nano composition to be utilized any time as per the need. The advanced technologies will shed light on several aspects of the characterizing methodologies employed for the analysis of nanoparticles for the determination of their toxic profiles. These techniques are also utilized to identify the physical and chemical properties at nanoscale.[220] The preparation of HNM can be upgraded by applying the various methods to achieve accuracy in the targeted transport of active substances. These analyses are quite capable to play a noticeable role in the innovation of the HNM. Therefore, it is quite possible to develop effective and well-tolerated remedies to treat incurable diseases.

Nanotools can acquire biological information easily, quickly, and inexpensively for proper analyses. These applications enormously complete the promises as projected at the time of designing of the nanotools or nanomedicine. The main objective is to innovate these tools for novel therapeutics and diagnostics that can altogether be performed as per the needs. These nanoscale tools are highly capable to perform for theranostics operations. The use of nanotechnology in diagnostic and therapeutic can be simultaneously applied to achieve the target.[221] The innovation of these nanomaterials is the necessity of the approach. Here these tactics can be applied to recognize cells and cell constituents. These tiny tools can identify genes of impaired function and can repair them at their consensus. These futuristic approaches were being researched in the context of herbal remedies. By introducing small molecules in a switch-on-switch-off mechanism could successfully implement it in a draconic engineered T cell therapeutic approach. Nanobiotechnology unlocks the alternative possibilities in HNM. These nanodevices can stimulate and detect the control of cell growth, damaged or absent tissue. These techniques can be employed for the analyses in cartilage, and bone. These multifunctional materials enhanced potential of HNM. These nanomaterials can stimulate the nerve cells, or regenerate it artificially.[222] Nanoporous carriers are now being used in wound healing and plastic surgery as matrices. These materials can control cell growth.[223] These tools can enhance the growth of nerve cells that can be employed in the treatment of incurable neurological diseases such as Alzheimer's, Parkinson's, epilepsy, and multiple sclerosis. These multifunctional materials can do manipulation in adult stem cells successfully. Intensive research is being conducted to know how various mechanisms of targeted transport of these nanomaterials can use to introduce nucleic acids, DNA fragments, and individual genes into the tissue. Nano-based gene therapy is aimed at the addition of missing and replacement of defective DNA. Therefore, nano-herbal interferes directly influence cell processes at the molecular level. The key features of the probability of repairing DNA eventually will also result in the capability of targeted manipulation of DNA, these areas stumbled in here. The aforementioned topics and research needs will be covered shortly. By considering these aspects, a futuristic layout may be developed for the innovation of more advanced HNM.

NEED FOR CLINICAL TRIALS FOR HERBAL NANOMEDICINES

To gain the patient's trust and to bring herbal nanomedicines into the mainstream of today's health care system, the researchers, the manufacturers, and the governing agencies must wipe on rigorous scientific methodologies. There is a need for rigorous clinical trials to confirm the quality and lot-to-lot reliability of these HNM. The scientific validation of the final formulation has not been well defined and also there are no purification steps involved in the productions of HNM. It directly affects the quality and consistency of products relies mostly on quality control of source materials and the manufacturing procedures of the final products. By using modern technologies, the quality and reliability of heterogeneous HNM can be developed. A well-designed clinical trial is a method of choice to find out the safety and efficacy of these therapies. Manufacturers of the herbal nanomedicines must adhere the necessities of good manufacturing practices and preclinical testing before these products can test on humans. The basic principle and design of clinical trials for HNM are the same as those for a single component chemical product. Several randomized double-blinded controlled studies have been carried out by using herbal formulations.[224] These studies have proven the efficacy of HNM, but the minor side effects were reported. Thousands of years of traditionally used herbal remedies can provide us valuable guidelines required for the selection, preparation, and application of these formulations. It is believed that these can be viable alternatives to western medicine, therefore, the same rigorous methods of scientific and clinical validations must be employed for these formulations too. It was believed that this HNM is worthy for the future and HNM formulation never notice as a substitute by approving them through clinical trials.[225] Several HNM has already been made, and substantially considered in the clinical studies. Several trials

on phytomedicine were reported, including the use of grape seed (Vitis vinifera L.) extract for the treatment of the diseases. Pharmaton in Switzerland, a subsidizer of clinical trials on ginseng (Panax ginseng), Schwabe of Germany, conducted many trials on St. John's wort (Hypericum perforation L.). Madaus, Germany, sponsored innumerable studies on Ginko (Ginkgo biloba L.). Lichtwer is well identified in the studies on garlic (Allium sativum L.). Nutrilite and Pharmanex in the US endorsed for the analysis of the saw palmetto [Serenoa repens (Bartr.) small] and red yeast (Monascus purpureus) respectively).

POLICY ISSUES

The concerned rules and provisions related to HNM development and their approval as a medicine vary in different countries and need separate interpretation of respective rules. It is one of weakness for application of these remedies. For example, there are unclear provisions for the assembly of natural product as drugs or when someone try to get desired collections outside the researcher's home country. Practically, it is a very complicated scenario. The legality of these facts sometimes deprives the efforts of researchers. Therefore, there is a need to cover the legal necessities to elaborate these needs. The legal procedures are generally time-consuming and uncomfortable for researchers. These necessities limit academicians and researchers, and lead to decline in interest. These hurdles may be removed by the implementation of the knowledge of taxonomy, ecology, and evolutionary biology. The provisions should include requirements and allow researchers to carry out the concerned research on natural products. These efforts will provide a platform for researchers to do research ethically within a settled legal framework. In this sense, it protects the institution or company intertwined from the concerns of bio-piracy.[226]

CONCLUSION

The engineering of nanoscale materials at the atomic and molecular levels shaped these multifunctional materials into numerous forms such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferases, and ethosomes. These nanocarriers are capable to transport the phytochemicals, bioactive, and plant extracts. These are the main constitutes of HNM formulation and displayed the amazing potential for enhancing solubility, bioavailability, reduce toxicity, pharmacological activity, stability,[10] capability for the delivery of value-added tissue macrophages distribution. These components governed the physical and chemical properties in the formulation of HNM, as illustrated in figure 7. These formulations have the desired abilities for which the researchers are looking for. The inbuilt constituents exhibited enormous potential by increasing selectivity and efficacy, shielding alongside thermal- or photo-degradation, less side effects, and monitoring the abilities of active constituents. These characteristics enhanced therapeutic varieties. These abilities are eye-catching and must be underlined during the implementation of HNM formulations.[227] These formulations and remedies are eco-friendly having bio-friendly natural-based phytomedicine,[228] phytochemicals, and pigments. These components have therapeutic values required for the prevention and cure of diseases as per the needs. These novel herbal remedies are incorporated in the nanoparticles, which were developed for the delivery of these phytomedicine and natural components. Nanopharmaceuticals reduce toxic impact and enhanced patient compliance. There are various nanoparticles (liposomes, polymeric nanoparticles solid lipid nanoparticles, magnetic nanoparticles, metal, and inorganic nanoparticles, quantum dots polymeric micelles, phospholipids micelles, colloidal nano-liposomes, dendrimers, micro-emulsions,

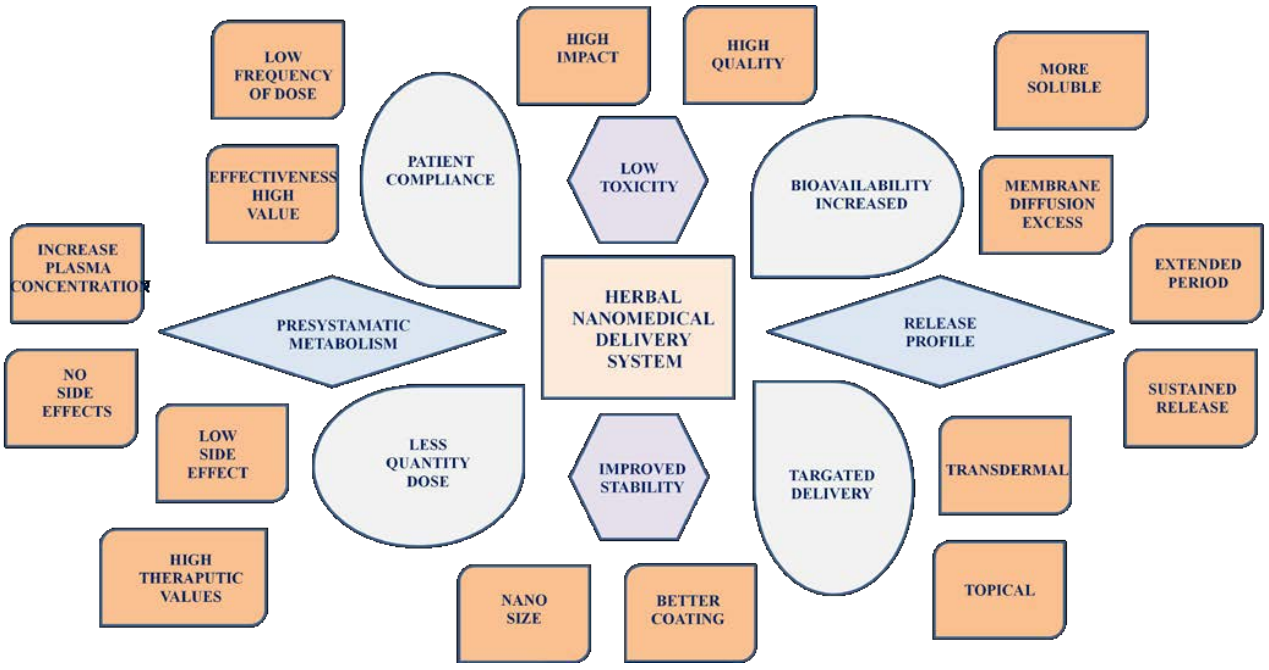

Figure 7. Schematic representation of herbal drug delivery system mechanism (enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery).

proliposomes, and solid lipid nanoparticles) which showed the potential to deliver phytomedicine.[229] The use of nanotechnology in the delivery of phytomedicine significantly increased in recent years. The rise of nanotechnology is to expect opening up fresh breaks for the formulation of the HNM. These have the potential to boost the pharmacokinetic and pharmacodynamic activity. By increasing bioavailability, these nanoparticles can enhance the percentage of the possibilities to cure the patients with a deadly condition.[230] For the authentication, there is a need for the logical tactic to be implemented to find out the importance of the bio-degradable nanoparticles in the preparation of the HNM formulations. Most of the HNM prepared from the herbal extracts, therefore, it may be problematic because there is no specific method available to date to identify the required compounds. Few of the chemicals that exist in these formulations can act as a reducing agent. Therefore, there is a need to identify these materials for a novel nano-biomolecule interface. These efforts may be accountable for the formulation of a better therapeutic.[231]

One more vital parameter is to predict and analyze the required dosage, quantity, quality, and ratio. These are more challenging aspects to design HNM along with the nanomaterials. Therefore, any persistent error may mislead parameters that are necessarily required for the perfect dose formulation. These confusions may create different forms of recommendation to evaluate dose ratio. This is the combination of a fixed amount of herbal remedies and multifunctional nanomaterials. To deal with such kind of difficulties, there is a need for accurate measurements and error-free procedures. There is a need for the enormous efforts to cover up these newly fangled challenges having pros and cons. To remove these hurdles, researchers must search for the substitute of those technologies responsible for defects that persist from ages in the herbal research. The new developments in current science have the potential to find solutions for these complications. These intelligent approaches defiantly answered these concerns. The desire to have a novel HNM as an upcoming therapeutic option must be filled. The question of the stability of this HNM during consumption will remain the biggest questions for the researchers. The main reasons for the stability are critical and any fluctuations in the physical and chemical properties alter the proposed outcomes. Whenever any nanoparticle foreordained for these kind of drug delivery, during the assembly, new interfaces originated. These interfaces will target the diseased sites. The size of these formulations is another vital concern that to be kept in mind until the final formulation of the novel remedy is not achieved for the biomedical persistence.[232] It is evident that the smaller the size of the HNM, it will provide a balanced interface. These topologies are very easily excreted. These kind of the investigations look superficial, but in reality, these factors affect a lot of the characteristics of the nanoparticles. These styles generate highly sensitive nanoscale tools. Therefore, these are extremely reactive and it may yield unevenly undesired effects at the molecular level. The probabilities of these happenings certainly changed the same physical and chemical characteristics of these nanoparticles. These characteristics are affected by the particle size. The smaller the particle size, greater the chances for a swift translocation in the tissue partitions. These features are specifically considered for metal nanoparticles. The bigger particle sizes withheld their clearance. Therefore, these recommendations must be followed and implemented in the designing of these HNM.[202] There are numerous possibilities to be considered for the healthy utilization of HNM. The choice of a particular herb needs to be considered as the main constituent source because they are having active constituent molecules. These aspects must be investigated properly before use. The selection criteria of these herbal remedies must be based on biological activity, structural advantages, conjugation potential, toxicity profile, stability, etc.[233] The selection criteria set for the selection of these constituents must be based on the firmness, appropriateness, and therapeutic significance of the herbal remedies. Even a more clear-cut and advanced method must be employed to recognize active gradients that exist in the herbal remedies. These components are liable for therapeutic significance. The use of nanoparticle in the synthesis of the HNM by using an entire crude extract of the plant has never been considered as an accurate scientific approach. These methodologies may fail due to the presence of the interfering constituents in the crude extract. These toxic components may form undesired effects to interfere and influence the medicinal properties of the HNM.[234] The successful trials of the transportation of the active phytochemicals and herbal remedies and their interfaces with the HNM concluded the importance of natural products and herb extracts in the form of HNM as natural sources. Nature will continue to be a major source of new structural leads, and effectively HNM development. A multidisciplinary collaboration may further explore these ideas.[235] The novel bioactive components can be optimized by using combinatorial chemistry and could be quite helpful in the development of HNM.[236] Clinical pharmacokinetics is one of the entitlements of the pharmacokinetic principles and utilized for the innovation of the harmless and actual treatment in a particular patient.[237] Nanotechnology has the potential and must be considered for piloting the route as an intelligent source because of their idiosyncratically small size that is very effective at the septic pathological zones.[238] By scrutinizing the affiliation between nanotechnology and herbal remedies, the use of nanotechnology enhanced the bioavailability enrichment of HNM extraordinarily. Therefore, it will be wide-open to implement it to encounter existing problems.[239,240]

ACKNOWLEDGMENTS

One of the authors (RK) gratefully acknowledges his younger brother Bitto for motivation.

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AUTHORS BIOGRAPHIES

Dr. Rajiv Kumar received an M.Sc. (Institute Topper) post-graduate with honors in chemistry from CCS University (1999), and a Ph.D. in Macrocycle (nature molecules) from the University of Delhi (2004). His group is specialized in Chemistry, Nanoscience, and Nanotechnology, Computational Chemistry, Molecular Modeling, Computational Nanotechnology, Computational models of Biomolecules, and Macromolecular, Apoptotic Pathways, Atmospheric Chemistry, Spectroscopy, Biomarkers. He has published 35 research articles, 02/02 book chapters/review articles, and 02 theses reviewed. His book entitled *"Nanotechnology and Nanomaterials in the Treatment of Life-threatening Diseases"* author(s), N. Kumar and Rajiv Kumar, published by Elsevier Publication 2013, covers the contents for researchers working in the areas of nanoscience and medicine, pharmaceutical industries, and practicing physicians as well as surgeons. Dr. Kumar has worked as c*o-investigator* in the research project sponsored by DRDO, Ministry of Defence, INDIA.

Dr. Munesh Sharma is an Ayurveda physician and is practicing at Ayurvedic Clinic and Arogya Nidhi (regd.) Delhi. She also worked for the Ministry of Ayush, India. His group is working on Improvement in research methodology such as basic differences between Ayurveda and modern science, Ayurveda and biomedical specialties, the holistic and integrative approach involving body, mind, and spirit should be considered for research, before starting the clinical studies; a complete knowledge about diagnosis of the disease, materials to be used, process to be adopted, and accurate dosage form is highly needed, the approach of personalized medicine should be followed during treatment and other research thrust are encouragement of research on Ayurvedic fundamentals, validation of Ayurvedic drugs with reverse pharmacology, evidence-based benefits of traditional approaches, encouragement of interdisciplinary research, improvement in quality of herbal drugs, active involvement of government, development of Ayurvedic pharma sector, up-gradation of Ayurveda literature, revalidation of clinical trials, combination of Ayurveda and western medicine, resolution of controversies in Ayurvedic drug, and improvement in personalized medicine with modern technology.