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NANO - STRUCTURED HERBAL ANTIMICROBIALS

Rachna Gupta*[1], Pramod W. Ramteke [1], Himanshu Pandey [2] and Avinash C. Pandey [3]

Department of Biological Sciences [1], Sam Higginbottom Institute of Agriculture, Technology and Sciences, Allahabad- 211007, Uttar Pradesh, India
Department of Pharmaceutical Science, Faculty of Health Sciences [2], Sam Higginbottom Institute of Agriculture, Technology and Sciences, Allahabad- 211007, Uttar Pradesh, India
Nanotechnology Application Centre, Faculty of Science, University of Allahabad [3], Allahabad- 211002, Uttar Pradesh, India

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Correspondence to Author:

Rachna Gupta

Department of Biological Sciences, Sam Higginbottom Institute of Agriculture, Technology and Sciences, Allahabad- 211007, Uttar Pradesh, India

E-mail: rachna3585@gmail.com

ABSTRACT: The use of traditional medicines of natural origin is being encouraged for the treatment of chronic disorders, as synthetic drugs in such cases may cause unpredictable adverse effects. The various strategies which have been identified to defeat drug resistance, the investigation of new and effective natural products exhibiting antimicrobial activity against pathogenic microorganisms is likely to play a significant role to overcome drug resistance. The numbers of global infections produced by bacterial strains that are resistant to single and multiple antimicrobial drugs are on the rise. With emerging trends in nanotechnology it has become possible to address the problems associated with potential natural products to be developed as antimicrobial drug. Nanomaterials can improve the pharmacokinetics, bioavailability, therapeutic index and specificity of plant origin drugs. By smartly designing nanoscale carriers, therapeutic value of natural products can be drastically improved, number of plant origin drugs can enter into clinical trials and antimicrobial resistance can be cured. Nanosizing led to increase solubility of components, reduction in the dose via improved absorption of active ingredient. Thus, nanonization improve the problem of antimicrobial resistance.

INTRODUCTION: One of the biggest challenges faced by global population in the field of medical and public health sciences is antimicrobial resistance. Over the past 30 years, excessive use antibiotics and widespread development of resistance in pathogenic bacteria is now a serious threat which needs global concern. The situation has worsened as antimicrobial resistance has undermined the infection treatments. With very limited resources the antimicrobial resistance in bacteria has to be investigated and on the basis of reliable susceptibility data, methods of rational treatments and ways of optimizing the antimicrobial agents should be explored.

The undesirable, severe side effects and emergence of antibiotics in pathogenic bacteria has triggered immense interest in the searching of new antimicrobials of plant origin [1].

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Paradoxically, as the problem of antimicrobial resistance is increasing, discovery and development of new antimicrobial is declining. Complex situation has arisen because identification of suitable novel compounds as antimicrobials is technically difficult [2]. As such, the discovery of drugs with novel modes of action will be vital to meet the threats created by the emergence of resistance. While antimicrobial resistance is rapidly spreading, research and development for new antimicrobial agents are languishing.

This review presents a novel approach for dealing with the problem of antimicrobial resistance by utilising natural plant phytochemicals and defining it according to the nanotechnological aspects of drug designing which will be beneficial for human beings for combating against antimicrobial resistance.

Miracle drugs to Super Bugs: A century ago when antibiotics came into use were considered as 'miracle drugs' and their popularity rapidly led to overuse. Due to uninsured quality and irrational use of antibiotics pathogens are losing their effectiveness against them [3]. Accumulation of resistance genes on plasmids that are replicated and passed between microbial cells is main reason behind rapid rise in drug resistant pathogens. Such multi-drug resistant (MDR) microbes are termed as 'superbugs' [4].

Almost 70% of current day infections are suspected to be due to drug resistance [5], alone U.S ranked 4th for death caused by bacterial infections. Reports shows over 50% of hospital bloodstream infections are incurred by Vancomycin Resistant Enterococci (VRE) and Methicillin Resistant *Staphylococcus aureus* (MRSA). Among the *Escherichia coli* (E. coli) isolates from India and China, less than 50% are susceptible to commonly used antibiotics (e.g., Cephalosporins and Ciprofloxacin) [6]. Getting around the resistance problem is not a straightforward matter as there are high regulatory barriers and low chance of clinical success [7-8]. To address these issues, recently revived efforts have been made by pharmaceutical companies to develop new antibiotics [3].

In 1998, the World Health Assembly adopted a resolution urging Member States to take action against it. To bring international attention to a growing antimicrobial resistance, the World Health Organization (WHO) selected antimicrobial resistance as the theme for World Health Day 2011. In order to deal with the problem a policy package was developed to combat with antimicrobial resistance. The policy suggests well structured finance plan, strengthening of laboratory capacity, uninterrupted access to essential medicines, promote rational use of medicines and most important from the research point of view is to foster innovations in research and development for new tools [9].

Phytochemicals or Bioactive compounds as Antimicrobials: Plants are huge source of natural diversity as they synthesize number of compounds of therapeutic value and have been used since ancient times for treating diseases. Infact, approximately two third of active ingredients used as drugs are derived from plants [10]. Herbal medicines are again centre of interest, reasons are [11, 12]:

i) Increase in the sale of herbal medicines in the last 10 years,

ii) The idea that what is natural can only be good,

iii) Herbal remedies are believed to be better than conventional drugs,

iv) No other solution for very complicated diseases and;

v) Wide range of diseases is treated only with herbal plants.

Plant produces array of compounds commonly known as phytochemicals or bioactive compounds and significantly shows *in vitro* antimicrobial activity [13]. Clinical microbiologists have two reasons to be interested in the antimicrobial from plants: Firstly, it is very likely that these phytochemicals are already easily being tested in humans and effective life span of any antibiotic is limited, so new sources especially plant sources are being investigated.

Secondly, the public is becoming increasingly aware of the problems with the over prescription and misuse of traditional antibiotics has made public more aware [14]. Phytochemicals with recognized antibacterial activity belong mainly to the following chemical structural classes: phenolics, terpenoids and other essential oils constituents, alkaloids, lectins and polyacetylenes. The major subclasses are: simple phenols and phenolic acids, quinones, flavones,

flavonols, tannins, coumarins, terpenoids and essential oils, alkaloids, lectins and glycosides [14, 15, 16]. For instance, *Emblica officinalis*, *Saraca indica* and *Terminalia arjuna* showed antimicrobial activity against various multi-drug resistant (MDR) pathogens and their antimicrobial activity has been attributed to various phytochemicals [17].

Numerous studies have been done for testing the antimicrobial activity of phytochemicals derived from plants. Some of them are given in **Table 1** which depicts the antimicrobial activity of different class phytochemicals and their effectiveness on the resistance pattern of various pathogenic organisms.

TABLE 1: SHOWING ANTIMICROBIAL ACTIVITY OF PLANT PHYTOCHEMICALS OR BIOACTIVE COMPOUNDS

Plant	Phyto-chemicals/ Bioactive compounds	Class	Activity against pathogenic bacteria	Resistance pattern of bacteria	Reference
Allium sativum	Allicin	Flavonoid	*Klebsiella pneumoniae* and *Bacillus cereus*	Carbenicillin, Ceftriaxome, and Gentamycin	18
Berberine vulgaris	Berberine	Alkaloid	*S. aureus and E. coli*	Cephalexin Ceftizoxime	19
Curcuma longa	Curcumin	Alkaloid	*S .aureus*	Gentamycin, Doxycycline, Ampicillin and Erythromycin	20
Emblica officinalis	Gallic acid	Tannin	*K. pneumoniae*	Carbenicillin, Ceftriaxome, Tobramycin, Gentamycin and Nitrofurantoin	17
Mangifera indica	-	Alkaloids and phenols	*E. coli*	Penicillin, ampicillin, methicillin,vancomycin, carbenicillin, erythromycin etc.	21
Ocimum sanctum	Eugenol	Terpenoid	*Shigella sonnei-10*	Penicillin, cefurco-trimoxazoleoxime, cefpodoxime, nalidixic acid, tetracycline etc.	21
Piper nigrum spp.	Piperine	Alkaloid	*S. aureus*	Ampicillin	22
Saraca indica	Epicatechin	Flavonoid	*E. coli*	Amoxicillin, Carbenicillin, Erythromycin, Penicillin, Tetracycline and Vancomycin	17
Terminalia arjuna	Luteolin	Flavonoid	*S. aureus*	Penicillin, Erythromycin, Methicillin and Clendamycin	17

Mechanism of action of Phytochemicals: Phytochemicals has potential to inhibit bacterial growth by different mechanisms than the presently used antibiotics. Multi-drug resistant (MDR) pathogens exhibit a plethora of antibiotic resistant mechanisms to strike back and nullify antibiotic actions including enzymatic alteration of antibiotics, modification or overproduction of targets, reduced drug uptake, metabolic bypass of the targeted pathway, extracellular active pumping of drugs and drug sequestering by protein binding [4]. **Table 2** shows the results of some of the exploratory studies on the phytochemicals mechanism of action for antimicrobial activity. These studies have shown that the site of action of phytochemicals on bacterial cell.

The allicin (diallyl thiosulfinate), a phytochemical commonly obtained from *Allium sativum* (garlic), has potent antimicrobial activity and inhibits RNA synthesis and intracellular interaction with thiols and thiol containing proteins [23, 24]. 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* [25, 26]. Similarly, reserprine inhibit efflux pump [27, 28, 29].

TABLE 2: MECHANISM OF ACTION OF SOME PHYTOCHEMICALS OR BIOACTIVE COMPOUNDS ON BACTERIA:

Phytochemical	Mechanism of action on the cell	Bacteria
Allicin	Inhibition of RNA synthesis and intracellularly interaction with thiols [23, 24]	*Salmonella typhimurium*
Berberine	Interaction with the cytoplasmic membrane with DNA [25]	*S. aureus*
Piperine and Reserprine	Efflux pump inhibition [26, 27, 28, 29]	*S. aureus*
Epicatechin gallate; Epigallocatechin gallate	Inhibition of bacterial type II fatty acid synthesis ; Efflux inhibitory activity [15, 23, 30]	MRSA; *E. coli*
Gallic acid	Permeabilization of outer membrane [31]	*Salmonella spp*.
Quercetin	Gyrase binding of *E. coli* DNA and inhibition of the enzyme's ATPase activity; membrane potential dissipation and permeability of the inner bacterial membrane increases [32, 33]	*E. coli*

Polyphenols, such as flavonoids (epigallocatechin gallate) can inhibit the synthesis of nucleic acids of both Gram–negative and Gram-positive bacteria by inhibition of bacterial type II fatty acid synthesis and efflux inhibitory activity [23, 30].

Epicatechin gallate and epigallocatechin gallate, two constituents of the major flavonoids found in green tea, inhibits antibiotic efflux pumps in methicillin-resistant *S. aureus* (MRSA) and *E. coli* [15, 23, 30]. Gallic acid, tannin inhibits permeability of outer membrane in *Salmonella spp*. [31]. Quercetin, a component of propolis, binds to GyrB subunit of E. coli DNA gyrase and inhibits the enzyme's ATPase activity [32, 33]. Studies are limited because of complex mechanism but it is clear from the different studies that phytochemicals has potential to combat with the problem of antimicrobial resistance as they can act on multiple biochemical targets of the bacterial cell.

Challenges in natural drug development from phytochemicals: Natural products offer powerful leads for therapeutic development because they have known effects on organisms. Various studies are being done for the exploration of mode of action of phytochemicals for antimicrobial activity. But problem arises in very initial stages like how to improve its competitiveness with synthetic drugs and combinatorial libraries [34], plant which shows potent biological activity have poor water solubility or very short circulating life and face significant development challenges [35]. Despite the challenges many natural drugs like artemisinin, curcumin, triptolide and capsaicin have been extensively studied and entered into clinical trials. Number of capable compounds stumble in obscurity [36]. Not only in natural drug selection and isolation, delivery of natural drugs using conventional dosage forms is also challenging.

Main reasons for problem in delivery of natural drugs are [37]:

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 to the clearance and metabolism before reaching to systemic circulation.

All these challenges exacerbate the problem of paucity of new antimicrobial agents.

Nanotechnology; A novel approach to herbal drug formulation and delivery: Keeping in mind the policy package of WHO i.e. to foster innovations in research and development for new tools [9], researchers diverted their insight by using nanotechnological approach in novel drug formulation and delivery.

Nanotechnology concerns the understanding and control of matters in the 1-100 nm range, at which scale materials have unique physicochemical properties including ultra-small size, large surface to mass ratio, high reactivity and unique interactions with biological systems [38]. The particles size and surface characteristics of nanoparticles can be used for drug formulation and controlled delivery.

Nanotechnology offers many solutions for overcoming the problem of bioavailability like, use of nanocarriers for herbal formulations and also encapsulation of insoluble compounds in soluble nanoparticles, which has potential to increase number of drugs in clinical trials [39].

Nanotechnology is also best for the delivery of drugs which are poorly bioavailable due to their unfavourable physicochemical or pharmacokinetic parameters. Apart from improving the bioavailability of the drug candidates, increasing targeting abilities consequently lowering the required dose and modification of conventional nanoparticles with ligands has the potential to increase therapeutic index and reduce side effects are few more advantages of using nanotechnology in drug formulation and their delivery [40, 41, 42].

Therefore, it can be stated that emerging trends in nanotechnology has made possible to address the problems and challenges associated with potential natural products to be developed as antimicrobial drug. By using nanoscale carriers, therapeutic value of natural products can be drastically improved and antimicrobial resistance can be cured. However, nanocarriers may not be suitable for all drugs especially less potent natural products. Because the higher dose of the drug would make the nanocarriers larger, this would be difficult to administered [43].

Nanonization of Herbal Drugs: In recent year, the nanonization of herbal medicines has attracted much attention [44]. Nanotechnology deals with the size from 1nm -100nm. However, particles varying size from 10nm- 1000nm are colloidal systems of nanoparticles and nanoemulsions [45, 46]. Nanoparticle systems with mean particle size well above the 100 nm standard have also been reported in various literatures [47, 48, 49, 50, 51]. **Table 3** shows the mean particle size of different herbal drugs.

TABLE 3: SHOWING SIZE OF NANONIZED DRUGS:

Nanonized drug	Mean Particle size
Nanonized curcuminoids [47]	450 nm
Paclitaxel [48]	147.7 nm
Praziquantel [49]	200 nm
Posaconazole [50]	Less than 200 nm
Trans cinnamaldehyde and Eugenol [51]	Less than 200 nm

On comparing with crude drugs extracts, nanonized antimicrobials possess many advantages, such as increased compound solubility, reduced medicinal doses, and improved absorbency of herbal medicines [52]. Nanonized herbal drugs are also bioactive molecules or biodegradable nanoparticles which has high bioavailability, solubility, retention time, efficacy, specificity, tolerability and therapeutic index of corresponding drugs. At the same time nanonized drugs reduce the patient's expenses, risks of toxicity and have many advantages such as the protection of premature degradation, enhancement of intracellular penetration and interaction with the biological environment [53]. Nanosizing led to increased solubility of components, reduction in the dose via improved absorption of active ingredient.

Nano-structured herbal antimicrobials: Various nano herbal antimicrobials like nanocapsules of *Zedoary* turmeric oil was found to have some antibacterial activity and anticancer effect as they showed improved stability and increased drug loading capacity [54]. Also, nanocurcumin of narrow particle size distribution in the range of 2- 40 nm was prepared and was found to be effective than curcumin against gram positive bacteria [55]. Similarly, nanoparticles formulation of paclitaxel and doxorubicin leads to the inhibition of drug resistance [56].

Eugenol and *trans*-cinnamaldehyde loaded nanoparticles formulations proved to be efficient in inhibiting growth of *Salmonella* spp. (Gram-negative bacterium) and *Listeria* spp. (Gram-positive bacterium) [51]. Recently, various nanonization strategies have emerged to increase the bioavailability of numerous drugs that are poorly soluble in water. Nanonization of drugs increases surface to volume ratio, change in crystalline form and designing novel nanomaterials which acts as carrier for controlled release and also decreases systemic side effects [57]. **Table 4** shows Patents of some nanonized herbal antimicrobials are also available [58].

Constraining challenge: Size of nanonized herbal drugs, lipid solubility and degradation in acidic stomach are some of the biggest constraining challenge as size of blood capillaries are very small and problems arises *in vivo* drug delivery of these nano herbal formulations though these possess excellent bioactivity *in vitro*.

TABLE 4: PATENTS ON PREPARATION OF NANO HERBAL DRUGS

US Patent no.	Original inventor	Filed on	Active ingredient	Title
US20110190399 [58]	Santosh Kumar Kar *et al*	July 31,2009	Curcumin	Curcumin nanoparticles and methods of producing the same.
US2011/0245258 [59] A1	Rajesh Jain *et al*/Panacea biotech ltd.	November 18, 2009		Novel antimicrobials
US20120222144 [60]	Daniel James Wahlquist	February 25, 2011		Novel garden beansb4474
US20130029905 [61]	Krishnakumar Illathu, Madhavmenon *et al*/ M/s Akay flavours and Aromatics Pvt., Ltd.	January 27 2012	curcuminoids	Formulation containing curcuminoids exhibiting enhanced bioavailability

CONCLUSION: In the current scenario, it is of the utmost importance to develop an efficient and nontoxic strategy to control microbial infections in humans. Herbal drugs/plant actives possess a lot of therapeutic potential. New technological advances and unmet clinical needs provide the key driving force for the research and development of nanonization strategies.

Major research efforts have been focused on the development of enabling nanoformulations technologies, to convert poorly soluble, poorly absorbed and labile herbal drugs into promisingly bio available herbal drugs. New pharmaceutical materials and quality control to improve product properties while reducing production costs are being introduced to inhibit multi drug resistance. Application of nanonization led to enhanced bioavailability of plant actives by increasing the permeability and solubility as well as reduction in side effects.

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