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Therapeutic analysis of *Terminalia arjuna* plant extracts in combinations with different metal nanoparticles

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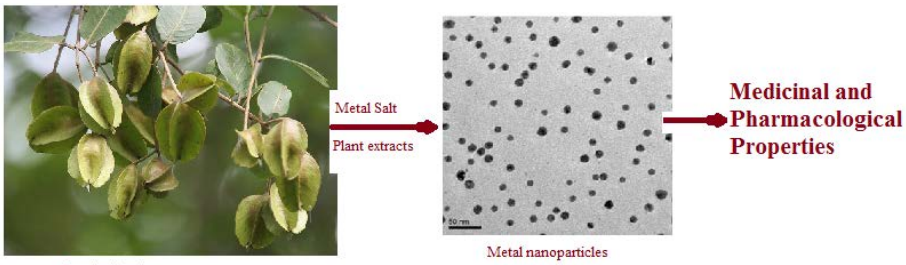
ABSTRACT



Terminalia arjuna commonly known as Arjuna is among the most valuable plants used in Unani, Ayurveda, Tibetian and Homeopathy medicine. Different plant extracts of *Terminalia arjuna* has been used for the synthesis of metal nanoparticles like gold, silver, copper, platinum, magnetic iron nanoparticles, self assembled gels and studied with silica gel incorporation. The present review discusses various metal nanoparticles synthesized, self assembly of constituents and their characteristics obtained using extracts of *Terminalia arjuna* along with progress towards pharmacological properties evaluation in extract combinations which are effective for controlling various kinds of ailments.

Keywords: Gel, Silver Nanoparticles, Gold Nanoparticles, Plant extract, Terminalia arjuna, medicinal properties

INTRODUCTION

Arjuna (*Terminalia arjuna*) is a 40-60 feet tall tree found in sub-himalayan, central and southern part of India. It is among the most valuable plants used in Unani, Ayurveda, Tibetian and Homeopathy medicine.[1,2] Its bark is a rich source of flavinoids like arjunoline, ajunone, phytosterol, anti-oxidants as well as good source of minerals like copper, zinc, calcium. Its phytochemical constituents are effective in treating asthma,[3] hypertension, ear infection, ulcer, liver problem, diabetes[4] and highly effective in LDL-cholestrol, ischemic heart diseases.[5-7]

A recent survey by World Health Organization showed that 80% of world population is dependent on traditional herbal medicines especially India and China like developing countries.[8] The traditional medicine find a quick healing strategy and handy tool for the remedy of various ailments, particularly their easy to reach to most of the population. The plant based medicines have widespread popularity and with no or negligible side effects, these therapies are being used as first step of treatment in Asiatic region. Further, culminated with modern science advances, the research has progressed in finding the active constituents of plants extracts responsible for particular therapeutic effect. The different natural products obtained in pure form are further being evaluated towards new applications in and using modern medical science.[9]

The recent advances in nanoscience and nanotechnology has proved a boon for the development of newer medical therapies and improving the potential of exisiting therapies.[10-12]

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Understanding the physcial properties of different materials at nanomolecular level led to development of better designed methodologies[13] and modelaties towards targeted therapies.[14] Developing constituents at nanometer scale using naturally occuring substances has gain impetus due to easy availability of materials and obtaining nanomaterial by green methods. The plant products particularly have served as an excellent source for synthesis of nanomaterials by easier methods.

Different plant extracts of *Terminalia arjuna* (figure 1) has been used for the synthesis of different nanoparticles like gold nanoparticles, silver nanoparticles and magnetic iron nanoparticles. The present review discusses various metal nanoparticles synthesis, superamolecular gel formation by constituent derivatives and their characteristics obtained using extracts of *Terminalia arjuna* and further progress towards their pharmacological properties evaluation in extract combinations.

Figure 1. Terminalia arjuna plant and parts

NANO SELF-ASSEMBLIES

Self assembly of the natural products or their derivatives is an intricate and intrigued phenomenona which is being studied with their possible applications in advanced nanoscience fields. Many constituents of the plant products (like steroids, terpenes, alkoloids etc.) posses polar groups and non-polar structure which can be utilized in their proper molecular interactions among the molecules of themselves (self assembly) under suitable conditions (like selective solvents, temperature etc.) to form the nanostructures or superamolecular arrangements (e.g. gels).[15]

The *Terminalia arjuna* is rich source of various terpenoids, flavones, steroids, glucosides, polyphenols, tannins, and other natural products. Derivatives of these chemical constituents are known to form nanoaggregates under different environmental conditions.

The mixture of the triterpenic acids extractable from *Terminalia arjuna* contains arjunolic acid as the major component. Another triterpene, the asiatic acid, having a close structural resemblance with arjunolic acid is generally obtained as a minor component and it has been isolated from mixtures by synthesizing its derivatives.[16] The arjunolic acid is having carboxylic acid at one end and trihydroxy group (glycerol mimic or glycol like plus one methylalcohol) at another end separated by non-polar carbon chain (figure 2).[17]

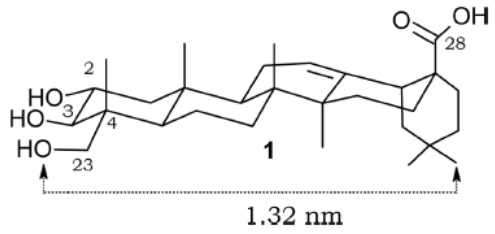


Figure 2. Structure of Arjunolic acid

Arjunolic acid (Figure 2), as such do not aggregate or self assemble in any solvent or form superamolecular gels, however, its synthesized derivative like arjuna-bromolactone (Figure 3) form nanoaggregates in aromatic organic solvents like mesitylene and o-xylene to form superamolecular organogels.[16] The gel formed is transparent (Figure 4 inset). The Scanning Electron Micrograph (SEM) images of dried gels (xerogels) indicated varying fibers of submicron diameter. Solid state structure of Arjuna-bromolactone revealed a 1D-helical self assembly indicating the specific mode of packing of the molecules within the fiberillar networks (Figure 4). The gel to sol temperature (T_{gel}) of these gels increased with the increase in concentration of arjuna-bromolactone which indicate increase in branching of fiberillar networks of gel (figure 4c).

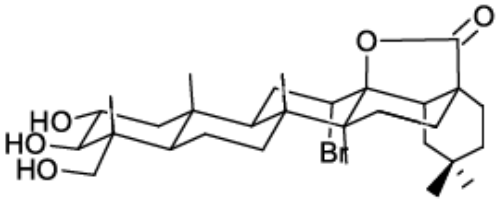


Figure 3.Chemical structure of Arjuna-bromolactone derivative of arjunolic acid

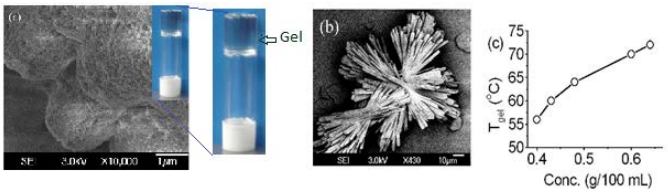


Figure 4.Scanning Electron Micrographs (SEM) image of dried gels of Arjuna-bromolactone in (a) mesitylene and (b) o-xylene. Inset of (a) contain inverted vial transparent gel. (c) Plot T_{gel} vs conc. (g/100ml) in o-xylene. Figure adapted from ref [16].

The molecules obtained by derivatization of hydroxyl group of arjunolic acid with aromatic groups form the transparent gels. The benzyl and nitrobenzyl derivatives (figure 5) of arjunolic acid form transparent gels in alcohols (methanol, ethanol and propanol) at varying concentration from 1% to 0.33% at room temperature.[18]

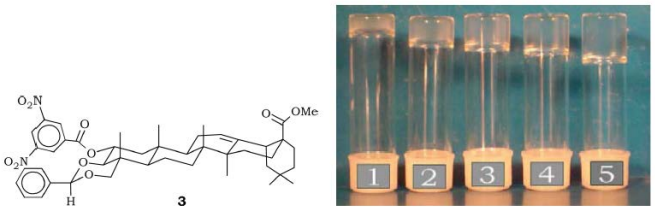
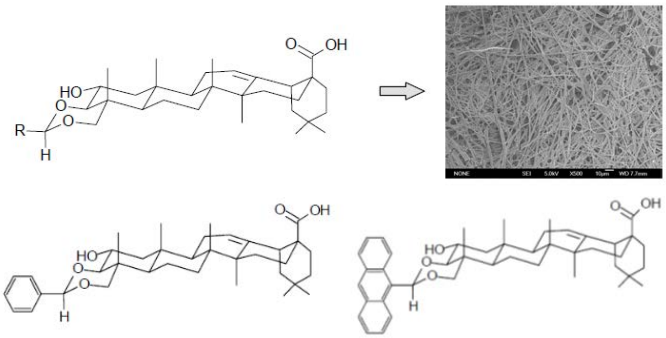


Figure 5. Organogels of benzyl derivatives of arjunolic acids in 2-propanol at different concentrations. Figure adapted from ref [18].

Monoaryl derivatives of Arjunolic acid also form organogels in aromatic solvents (Figure 6).[19,20] The synthesized monoaryl derivatives obtained by reacting benzaldehyde, anthraldehyde and other aromatic aldehydes with arjunolic acid (to make acetal) form transparent organogels with different aromatic solvents.[20]



R=benzo, 9-anthraceno and other aromatic groups
Figure 6. Chemical structure of reported derivatives and SEM of dried gels of benzoarjunolic acid in o-xylene. Complete structure of representative Benzo and anthro derivatives of arjunolic acid. Figure adapted from ref [20]

Compound benzo-arjunolic acid formed colorless gels mostly with aromatic solvents including toluene, o-xylene, m-xylene, p-xylene, chlorobenzene, bromobenzene, benzylchloride etc. In most of the aromatic solvents, gels were very stable for several weeks. The compound benzo-arjunolic acid was very efficient gelator at a very low concentration. For instance, toluene could be gelated with only 1.7% (w/v) of this compound indicating that a single gelator molecule is capable of immobilizing more that 423 solvent molecules. Compound anthraceno-arjunolic acid also show gelation in most of organic solvents. The other aliphatic derivatives, and aromatic derivatives with electron withdrawing group showed no-gelation in organic solvents. The gels with benzo-arjunolic acid and anthraceno-arjunolic acid possess firbrous and tubular structures on gelation in defferent solvents (figure 6).

GOLD NANOPARTICLES

Gold in nanoparticles size have unique physical properties like spectroscopic properties, conductance and surface plasmon which depend upon the size and morphology of nanoparticles. Gold nanoparticle [Au NPs] find applications in various fields like medical diagnostics, conductor chips, and environmental monitoring besides biomedical fields.[21]

The chemical synthesis of gold nanoparticles involve reduction of Au^{3+} salt (generally $AuCl_3$or $HAuCl_4$) to Au with simultaneous size stabilization (capping) of nanoparticles.[22] The size and stability of nanoparticles depends upon the rate of reduction and amount and properties of capping agents. This gold nanoparticle synthesis process can be accomplished by various plant extracts as plants are rich source of various pyrogallols, acids and other natural products which reduces as well as stabilizes the nanoparticles. This green approach using plant extracts is preferred due to being economical, easy and non-hazardous.

Terminalia arjuna plant have varous terpenoid, triterpenes, flavnoids, pyragallol etc and can be used for the syntheis of nanoparticles. The aqueous extract of *T. arjuna* fruit and fruit pericarp has been used as a reductant to synthesize AuNPs.[23,24] The aqueous extract of *T. arjuna* acted both as reducing and capping agent. By changing the quantity of *T. arjuna* aqueous extract, the reduction time, size and morphological changes occurred in gold nanoparticle (figure 7).

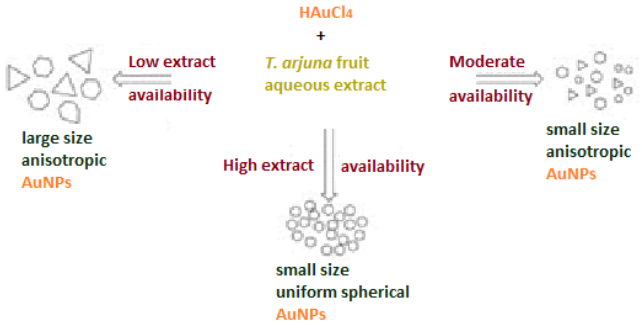


Figure 7. Size and morphology control of gold nanoparticles by change in amount of plant extract. Figure adapted from ref [23]

The nanoparticle size decreased as the amount of extract was increased as this help in reduction as well capping. AuNPs of desirable size can be achieved by varying the quantity of the extract. Uniform spherical NPs may be achieved at higher quantities of extracts. Lower quantities of extracts lead to the formation of larger sized anisotropic AuNPs. The synthesis of gold nanoparticles using lesser amount of extract led to triangular and hexagonal shaped larger sized AuNPs. With the moderate amount of extract, the naoparticle size decreased with triangular, hexagonal and spherical shaped AuNPs. When the extract was present in large amount, the uniform spherical small sized AuNPs were obtained (figure 7). Electrostatic interaction of carboxylic groups on the NPs' surface and the number of carboxylic groups available may be key in controlling the size and shape of the AuNPs. The colour change from yellow to ruby red indicated the formation of AuNPs. This visual colour change was due to surface Plasmon resonance of gold colloids (around 527nm). Anisotropic nanoparticles have surface plasmon in NIR region (can be used for selected bioimaging applications) while uniform spherical showed resonance around 527nm.

Terminalia arjuna leave extract has also been used for the formation of gold nanoparticles.[25] The nanoparticles obtained were 20-50 nm spherical crytalline structures having surface plasmon resonance at 530nm. The gold nanoparticles so obtained were found to induce the mitotic cell division of *Allium cepa* root

tip cells without any cytotoxic effect on root tip cells. The gold nanoparticles also increased the *Gloriosa superba* pollen grains yield.

The gold nanoparticles has also been reported from *Terminalia chebula* plant extracts.[26]

SILVER NANOPARTICLES

Nanometer sized silver metal particles are well known for their antibacterial and antifungal properties.[27,28] The silver nanoparticles synthesis involves the reduction of silver salts (Ag^+), generally $AgNO_3$ or AgCl, in presence of stabilizing/capping agents (surfactants or other carboxylic group containing natural products).[29]

Yallapa et al has reported synthesis of silver nanoparticles by using aquous extract of *Terminalia arjuna* bark.[30] As it was case with gold nanoparticles, similar reduction of $AgNO_3$ occurred in presence of polyphenols of extract and silver nanoparticle thus formed were stabilized by gallic acid and similar other extact compounds. The size of silver nanoparticles obtained was 10-20 nm. The surface plasmon observed by UV-Vis spectroscopy at 430nm indicated formation of silver nanoparticle in 50 seconds after mixing of silver salt and bark extract (figure 8).

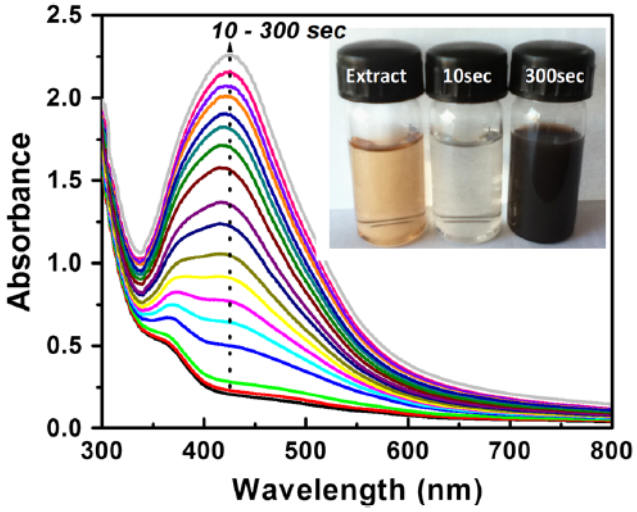


Figure 8.UV-vis spectrum of mixture and (inset) change in color of mixture indicating formation of silver nanoparticles with time (at 10 sec and 300 sec). Figure adapted from article by Yallapa et al. [30]

When isolated polyphenols from bark extract were used for the synthesis of nanoparticles, the reaction rate was high as nanoparticles formation took place within 10 seconds, however the nanoparticles agglomerated due to absence of capping agents. The silver nanoparticle obtained by extract method were stable for longer time (more than 3 months) due to presencce of other phenolic acids and other natural products as stabilizer. The nanoparticles were spherical in shape as indicated by FE-SEM. The bark extract synthesized AgNPs exhibit bactericidal activity for both gram-positive and gram-negative bacteria including multidrug resistant strains. The bare AgNPs (i.e. nanoparticle synthesized by isolated polyphenols without bio-capping) showed less activity when compared to as bark extract obtained AgNPs, while *T. Arjuna* bark extract alone showed least activity. This indicated that the plant residue adsorbed on AgNPs enhanced the antimicrobial activity. It may be due to the synergetic effect of AgNPs and capping molecules from extract. The bark extract bio-capped AgNPs showed enhanced antimicrobial and antioxidant property when compared to bare AgNPs. The AgNPs are known for their significant radical scavenging activity, so the bark extract synthesized AgNPs showed good antioxidant property.

The extract from *T. chebula* has also been utilized for synthesis of AgNPs and have been evaluated with better antibacterial, anticancer and chemical reduction applications.[31,32]

IRON NANOPARTICLES

The iron nanoparticles are new useful entities for material and biomedical applications as these posses exceptional properties like superamagnetism, high coercivity etc.[33] The biomedical application of iron nanoparticles mainly orient towards utilization of their magnetic properties like in magnetic resonance imaging (MRI).[34,35] The synthesis of iron nanoparticles by chemical synthesis or other methods results in nanoscale zero valent iron particles (nZVI) or iron oxide nanoparticles. nZVI (generally as a result of chemical and physical synthesis) are highly reactive in nature and tend to form aggregates, which lead to loss of their activity. The iron oxide nanoparticles can be obtained by mild reducing agents and along with natural capping agents (instead of surfactants) would be preferred for biomedical applications.[36]

Kumar et al. synthesized stable iron FeO (Wuestite) using aqueous extract of *Terminalia chebula* dry fruit pericarp and mixing it with $FeSO_4.7H_2O$. The formation of iron nanoparticles was indicated by colour change from light yellow to dark brown (reaction took place instantaneously). The synthesized nanoparticles were pure ironoxide (confirmed by energy dispersive X-ray spectroscopy (EDS)) and stable up to 21 days. The polyphenol and phenolic acid phytochemicals in the extract acted as reducing and capping agent.[37] The formation of nanoparticles was further indicated by surface plasmon at 575nm (for FeO) in UV-vis spectrum (figure 9 UV-vis spectrum C). The red shift in absorption (generally 527nm and 544nm) for FeO may be due to presence of polyphenols as capping agents. The amorphous nanoparticles were less than 80nm and spherical in size as observed by TEM (figure 9).

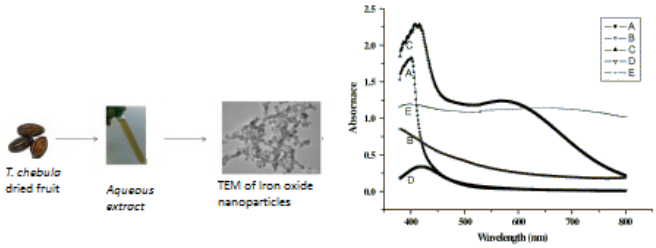


Figure 9. Iron oxide nanoparticles TEM and UV spectrum (A: *T. chebula* fruit aqueous extract, B: $FeSO_4.7H_2O$ control C: reaction product iron NPs obtained from the mixture of $FeSO_4.7H_2O$ and *T. chebula* extract, D: $PdCl_2$ and E: reaction product Pd NPs obtained from the mixture of $PdCl_2$ and *T. chebula* extract. Figure adapted from ref [37]

PALLADIUM NANOPARTICLES

Kumar et al. also reported the synthesis of palladium nanoparticles using aquous extract of *T. chebula* fruit pericarp and its reaction with $PdCl_2$ at room temperature.[37,38] The nanoparticles were formed within 40 minute of mixing as indicated by color change of solution from yellow to black, as supported by absence of absorption at 425nm (for $PdCl_2$)(figure 9). The nanoparticles obtained were spherical in shape and less than 100nm in size.

COPPER NANOPARTICLES

The Cu, Ag and Au are in the same group of periodic table (having similar structural/fcc and chemical features), still, the Cu nanoparticle [CuNPs] synthesis and its uses has not been explored to the extent as that of Ag and Au. Also the synthesis of stable metallic CuNPs is challenging because Cu^0 undergo rapid oxidation in ambient condition, especially in aqueous media.[39]

CuNPs are used as catalysts, sensors, electrochemical devices, photonic devices, heat transfer fluids, antibacterials and other biomedical applications. The CuNPs have been synthesized by different approaches viz., micro-emulsion/reverse micelles, laser irradiation, thermal decomposition, and chemical reduction. The bio-synthesis of CuNPs using the plant extracts/bioextract[40] is often considered superior as extracts contains metabolites such as flavonoids, proteins, terpenoids, tannins, polyphenols, etc. which not only acts as reducing agents for metal ion reduction but also (remains on the metalNPs) as capping agents which helps to minimize the agglomeration of NPs thereby controlling the morphology and also helping to protect/stabilize the NPs, thus improving the biological potential.[41]

The synthesis of CuNPs using aqueous extract of *T. arjuna* bark has been reported by Yallapa et al.[42] The CuNPs were synthesized by mixing the aqueous bark extract with $Cu(NO_3)_2$ followed by microwave irradiation. The starting yellow mixture turned to dark brown indicating the formation of CuNPs (figure 10) as indicated by UV spectrum (CuNP surface plasmon at 535nm). This indicates the reduction of Cu^{2+} to Cu^0 as Cu^0 particles solution imparted such a color change while there was less color change on the irradiation of plant extract alone (no SPR at 535nm).

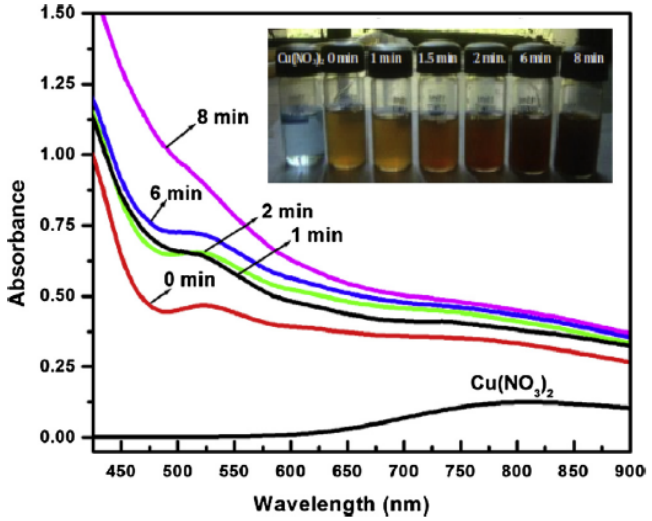


Figure 10. Formation of CuNPs and UV-vis spectrum at different time intervals of MW irradiation. Adapted from ref [42].

The synthesized CuNPs contained only Cu^0 particle and no oxides of Cu (CuO, Cu_2O etc). The nanoparticles were spherical in shape with 20-30nm diameter. FTIR spectrum indicated the presence of flavonones and terpenoids over the surface of CuNPs (further confirmed by NMR spectra), which might be acting as capping agents. The biomolecules present on the CuNPs surface prevent agglomeration of nanoparticles and thus keep the particles solution stable for long time (called as *in-situ* bio-capping of nanoparticles).

CuNPs so obtained have been evaluated for their antibacterial and antioxidant properties. The bio-capped CuNPs displayed higher anti-bacterial activity against *E. coli* and *S. aureus* and less effective against both *P. aeruginosa* and *S. typhi*.

The antioxidant activity measured by DPPH (a stable nitrogen centered free radical) test[43] showed color change (violet to yellow/colorless) with CuNPs. The antioxidant property of CuNPs is expected as these can get oxidized to Cu^{2+} in presence of oxidants (Cu^0 + DPPH → Cu^{2+} + 1,1-diphenyl-2-picryl hydrazine), thus can quench the free radicals and this way makes them suitable for sensor applications and as antioxidants and as suitable cancer prevention agent.

SILICA NANOPARTICLES

Nanoparticular sized silica or porous silica gel with large surface area have served effective medium for adsorption/entrapping and release of different drugs.[44] The low cost availability and easy synthesis of silica nanoparticles makes them material of choice for biomedical applications. It has been used for many synthesized drug molecules but there are very few reports on utilization for plant extracts.

Porous Silica gel has been used for entrapping extract of *Terminalia chebula* plant and then evaluated for antibacterial biological activities by Das et al.[45] The sustained release of extract components over the time provided good antibacterial activity and this was supported by mechanism of release[46] of extract components from silica nanoparticles. U.V visible spectroscopy showed 49% release of gel entrapped extract from the pore after 240hr, however, by weight loss method it was only 29% of the extract that was released from the porous silica gel. The silica gel could be used as control release system. MIC value of *Terminalia chebula* was 0.04mg/ml against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.

NANOTHERAPEUTIC POTENTIAL

During the synthesis of nanoparticles or nanoconjugates/nanosystems, the isolated plant products or selected plant products in very less amount are present in most of systems discussed above. The self aggregates or nanogels are from isolated or chemically modified triterpenes (arjunolic acid) and have not been studied for therapeutic applications.

The gold nanoparticles obtained using *T. arjuna* plant extracts have been sudied for their application in isolated form (with very less amount of extract as capping agent). The silver nanoparticles obtained using bark extract have nearly 30% of plant products as capping agents (as indicated by Thermal analysis).[30] In case of silver nanoparticles, the extract synthesized AgNPs having bio-capping showed better antibacterial, antifungal and antioxidant

properties compared to naked AgNPs or plant extract alone. Similar results have been recorded with copper nanoparticles (CuNPs), the naked CuNPs show negligible antibacterial activity while bio-capped CuNPs have better antibacterial activity. This indicate that there is synergistic effect of nanoparticles and biomolecules present as capping agents towards biomedical activity. These studies have reasonable potential as only selected biomolecules (and that as well get modified during synthesis of nanoparticles as these may be participating in reduction reaction and get oxidised themselves) from extract and in limited amount of extract (30-40%) are present on the surface of nanoparticles. The delivery of all extract components by using any of these nanoparticular systems by enhancing the loading would provide complete rational about the possibility of application or proper improvement of therapeutic potential towards particular biomedical application.

The porous silica gel has mainly been used for entrapping the plant extract and evaluated with comparative effectiveness of conjugate over pure extract toward its antibacterial activity. However, this system proved inefficient as only approx. 29% of the entrapped or adsorbed extract over the porous silica gel could be released over long time. Further, the report is lacking in proper evaluation about which of the components released and which left behind. The modification or strucure design changes in silica gel nanoparticles or using polymer nanoparticles should also be included in release studies of plant extracts.

The reports with *T. arjuna* and metal nanoparticles or other nanosystems have *in-vitro* studies only, the *in-vivo* evaluation need to provide the potential of possible application of observed enhanced activites. Also the toxicity studies, an essential parameter required for changed properties of extracts are lacking in reports.

There are isolated and very few reports on systematic evaluation of nanosystems with plant extracts, and particularly the evaluations are not for the main therapeutic effect a particular extract known for. e.g. the *T. arjuna* bark is mainly known for its antidiabetic and cardiovascular application, however, there are no report on using nanosystem along with bark extract for these ailments. A comprehensive and systematic study addressing these points might bring better outcome.

CONCLUSION

In conclusion, the various metal nanoparticles have been synthesized by using different extracts of *Terminalia arjuna* and reported to have been studied for different applications. The progress towards pharmacological properties evaluation in extract combinations which are effective for controlling various kinds of ailments, should be evaluated. The plant extracts has been used for the synthesis of nanoparticles and then isolated nanoparticles, generally, has been used for different applications. The studies should orient towards evaluation of combinations of nanoparticles or other nanosystems and plant extracts to check whether combinations are more effective compared to extracts alone, particularly the enhancement or application evaluation towards known treatmens should be on emphasis before newer application evaluation.

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