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Review Article

Approaches to Improve Solubility, Stability and the Clinical Potential of Andrographolide: A Review

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ABSTRACT

Andrographolide (AGL) is an active phytoconstituent of *Andrographis paniculata,* which is chemically a diterpenoid lactone ring. The various pharmacological activities of this compound are reported but a clinically remarkable effect was not observed due to their poor aqueous solubility and instability in different physiological conditions. This review comprises different approaches to enhance their solubility, stability and bioavailability of various physical and chemical modifications were made with Andrographolide. The nanotechnology-based approach in formulation shows the significant result to improve the characteristics of phytoconstituents. So various Formulations were developed like Nanoparticles (NPs), Liposome, Nanoemulsion (NE), etc. which multi-fold increases the solubility of AGL. In the modern era along with stability and solubility of the drug, controlled release pattern and targeted drug delivery is also major concern. Therefore, various novel formulations were developed by using a combination of two system approach to enhance safety and efficacy were comprised in the review. This dual approach gives a better therapeutic response as compared to a single nano-carrier system-based approach.

Key words: Andrographolide, Bioavailability, Nanocarriers, Solubility, Stability, Dual approach.

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INTRODUCTION

There are several medicinal plants that are used in the Indian traditional health care system from ages to treat various abnormalities. In these *Andrographis paniculata* belongs to the Acanthaceae family, which is also called Kalmegh,[1] a widely used plant for several viral infections. *Andrographis paniculata* has Andrographolide (AGL) as a major phytoconstituents which is a chemically diterpenoid ring.

AGL is reported for anti-microbial,[2] anti-inflammatory[3] hypotensive,[4] anti-diabetic, antioxidant activity, and hepatoprotective activity.[5] Xu *et al*. 2006 define the activity of the *Andrographis paniculata* against nine bacterial species including *Salmonella typhimurium, Escherichia coli, Shigella sonnei, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumonia, Streptococcus pyogenes, Legionella pneumophila,* and *Bordetella pertussis*. Chao *et al*. 2011 depicted the anti-inflammatory effect of *Andrographis paniculata* was observed by the significant inhibition of NF-κB luciferase, tumor necrosis factor (TNF-α), interleukin 6 (IL-6), macrophage inflammatory protein-2 (MIP-2), and nitric oxide (NO) secretions from lipopolysaccharide /interferon-γ. Thakur *et al*. 2016 observed the antidiabetic effect of acetylcholinesterase activity in the pre-frontal cortex and hippocampus of diabetic rats was 2.1 to 2.6 times higher compared to non-diabetic rats it exhibited that Andrographolide reduced acetylcholinesterase activity, oxidative stress, and insulin deficiency.

PHARMACOLOGICAL ACTION

Wound healing

AGL plays a significant role in wound healing. The pharmacological mechanism behind wound healing is the higher epithelisation rate, Up-regulation of human collagen I expression, Stimulation of formation of collagen fiber, Proliferation, and angiogenesis of tissue.[6] AGL has multidimensional approaches for the effective management of wound healing. Various healing mechanisms associated with AGL are shown in Figure 1. It creates pharmaceutical attraction for the development of topical formulation.

Anti-inflammatory activity

AGL significantly inhibits the NF-κB luciferase, tumor necrosis factor (TNF-α), interleukin 6 (IL-6), macrophage inflammatory protein-2 (MIP-2), and nitric oxide (NO) secretions from lipopolysaccharide / interferon-γ, as a result, a potent anti-inflammatory effect was observed in an animal model.

Hepatoprotective

AGL has a potent hepatoprotective action.[7] Stimulation of Glutathione level, inhibition of lipid peroxidase, and free radical scavenging activity is the major pharmacological pathway of AGL, to protect and strengthen hepatic cells[8] shown in Figure 2.

Various pharmacological models like carbon tetrachloride, galactosamine, lipopolysaccharide,[9] *Plasmodium berghei*,[10] paracetamol-induced liver toxicity[11] were developed to establish the hepatoprotective action of AGL.

Antiviral activity

Andrographis paniculata were also reported for antiviral activity against herpes simplex virus (HSV), HIV, flaviviruses, and pestiviruses. AGL increases the level of $CD4^+$ lymphocytes which significantly increases the immunological response which is weakened by the HIV virus.

Antipyretic and analgesic activity

Andrographis paniculata extract consists of a series of active phytoconstituents like phenolic acids, flavonoids, triterpenes, terpenoid

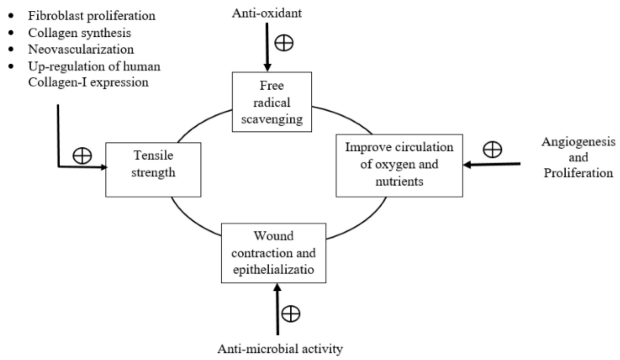

Figure 1: Wound healing activity of Andrographolide.

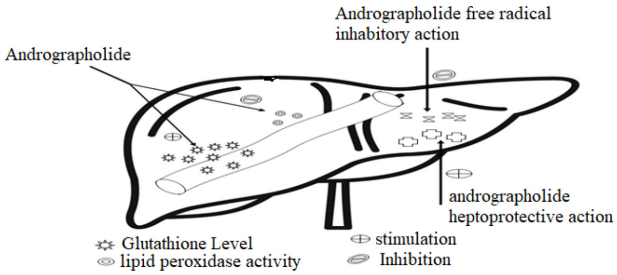

Figure 2: Hepatoprotective action of Andrographolide.

lactones, and volatile compounds. Various studies on animal models exhibited that terpenoid lactones and flavonoid shows antipyretic and analgesic activity.[12,13]

Antibacterial activity

Andrographis paniculata is effective against nine bacterial species including *Salmonella typhimurium, Escherichia coli, Shigella sonnei, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumonia, Streptococcus pyogenes, Legionella pneumophila,* and *Bordetella pertussis*.

Antidiabetic activity

AGL is effective against both type I and type II diabetes.[14] A recent study on gene expression reveals that AGL increases the hepatic apelin gene expression as a result the levels of blood glucose significantly decrease in blood plasma.

Anticancer activity

Many clinical studies exhibited that AGL has anticancer activity. Various mechanisms were suggested for their anticancer effect shown in Figure 3. Researchers depicted that up-regulation of tumor suppressor elements and down-regulation of tumor progression elements is the characteristics pathway followed by AGL to represent their anticancer activity. Down-regulation of cell cyclin protein CDK4 and up-regulation tumor necrosis factor caused by AGL is a selective mechanism behind the anticancer activity.[15] The Anticancer activity of AGL was observed by the induction of apoptosis.[16] Chao *et al.* reported that down-regulation of cell growth, apoptosis, anti-angiogenesis, and anti-transformation is the major pathway of AGL to inhibit cancer cell growth.[17]

Lim *et al.* exhibited that down-regulation of tyrosine kinase, cyclin kinase, and growth factor and up-regulation of Apoptotic protein is the potential mechanism of AGL against cancerous cells.[18] Kumar *et al.* reveal that down-regulation of cell proliferation shows significant anticancer

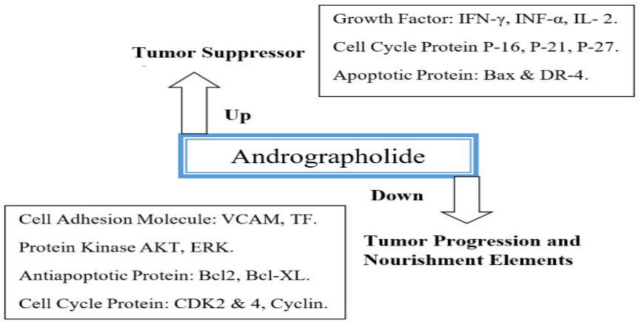

Figure 3: Anticancer/Antitumor activity of Andrographolide.

activity in HT-29 (colon cancer) cells.[19] Jada *et al.* also exhibited anticancer activity of AGL against breast cancer cell line (MCF-7) and colon cancer cell line (HCT-116).[20] Song *et al.* reported the anticancer activity of AGL against breast cancer cell line (MCF-7), Human colon cancer (HCT 116), and Human prostate cancer (DU 145).[21] The basis of various clinical studies of AGL on different cell lines exhibited that up-regulation of tumor suppressor elements like growth factor, cell cycle protein, and apoptotic protein, and down-regulation of tumor progression and nourishment elements like cell adhesion molecule, an anti-apoptotic protein, and protein kinase is the key factor to control abnormal growth of the cell.

Various clinical studies reveal that AGL has many pharmacological actions however, AGL was not depicted expediential therapeutic response due to their poor bioavailability and stability.[22] AGL exhibited poor absorption and low bioavailability during oral administration. The major cause of AGL instability are First-pass metabolism, gastric instability hydrolysis in weak basic medium, biliary excretion, terminal intestinal P-glycoprotein excretion.[23] Poor aqueous solubility and high lipophilicity are the major cause for poor bioavailability.[24]

The major concern behind the designing of drug delivery system is to improve stability as well as solubility of AGL. Localized delivery minimizes the first pass and pre-systemic metabolism of AGL and enhances the therapeutic potential.[25]

Topical application has site-specific drug delivery and also becomes patient compliance in case of wound healing. The therapeutic effect of topical preparation is limited by slow penetration or release of drug from the system at the wound. To overcome this hurdle various pharmaceutical approaches were made to improve the solubility, permeability, and bioavailability of AGL. Various nanotechnology-based drug delivery systems like liposomes, nanoparticles, nanospheres, nanofibers, nanocapsules, nanoemulsions, nanosponges, etc were developed to improve stability, solubility, entrapment efficiency, and potency of AGL[26] given in Table 1. Different nanocarriers were designed and optimized by the researchers but still, challenges are present to get a desirable response. Dual approach was incorporated to overcome the limitation present in the available drug delivery system.

DUAL APPROACHES BASED DRUG DELIVERY SYSTEM

Cyclodextrin based nanocarriers

In this novel approach, cyclodextrin combines with the nanocarrier to improve entrapment efficiency, solubility, and stability of phytoconstituents.[27]

Cyclodextrin is a stable macromolecule derived from the enzymatic degradation of starch. It has a cage-like structure with have lipophilic inner cavity and hydrophilic outer surface. They are water-soluble

Table 1: Various approaches for enhancement of solubility, bioavailability, and stability of Andrographolide.

Formulation	Composition	Method of Preparation	Characteristics	Key finding	Ref.
			Liposome		
Mannosylated Liposome	Phosphatidylethanolamine, cholesterol, diacetyl phosphate: AGL	Film hydration	Drug entrapment 46% in multilamellar vesicles (MLV) liposomes.	The mannosylated liposomes improved the efficacy of AGL as a result 86% reduction in splenic parasitic (Leishmania donovani amastigotes).	51
Herbosomes	Andrographolide-soya phosphatidylcholine	Rotary evaporation	Size in the range of 400–500 nm	Hepatoprotective potential and better absorption	52
Niosomes	Span 60 and Cholesterol	Film hydration	Drug entrapment 72.36%, Drug loading 5.90%, and Size 206 nm	Improve 2.14-fold liver targeting, reduced Andrographolide elimination. Hepatocellular carcinoma (HCC) activity of AGL in HepG2 cells.	53
			Solid Lipid Nanoparticles (SLN)		
SLN	Glyceryl behenate and Glyceryl-monostearate lecithin and Tween-80	Cold high-pressure homogenization	Drug-entrapment efficiency 91%, Drug loading 3.49%, Size 286.1 nm	2.41-time improvement in oral bioavailability of AGL as compared to pure AGL suspension.	54
SLN	Cetyl alcohol, Tween 80 Polyvinyl Alcohol, and Ethyl alcohol	Solvent injection	Sustained drug release 77.89% w/v of AGL up to 36 h. Size154.1 ± 10.7 nm	3.4 and 3.9-fold improvement in oral AUC and C_{max} respectively in rats.	55
			Polymeric Nanoparticles (NPs)		
AGL-loaded pH-sensitive Polymeric NPs	Eudragit EPO and Pluronic F-68	Nanoprecipitation	Drug entrapment 93.8 ± 0.67 %, size 255 ± 9 nm	2.2 and 3.2-fold increase in oral AUC and C_{max} respectively with 121.53% increase in relative bioavailability in Rat.	24
PLGA NPs	Poly D, L-lactide-co-glycolic acid (PLGA)	Emulsion solvent evaporation	Drug Entrapment 80%, Size of 173 nm	5 to 8 times more efficacious than pure AGL against monocyte-macrophage cells infected with the leishmanial pathogenic amastigote.	57
Chitosan-coated AGL-PLGA NPs	Chitosan, PLGA	Emulsion solvent evaporation	Drug entrapment 80.42%, size 173 nm.	An *In-vivo* study confirmed that the NPs reduced tumor weight by 68.21% as compared to 24.7% by pure AGL. Increased the life span of mice infected with Ehrlich ascites carcinoma by 78.08% as compared to 23.5% for pure AGL.	58
Heparin functionalized AGL loaded PLGA NPs	Heparin, 1% w/v pluronic F-127 and PLGA	Emulsion solvent evaporation	Drug entrapment 83.42%, size 181 ± 12.60 nm.	Effective for hepato-protection in paracetamol-induced acute liver failure.	59
Amphiphilic triblock copolymeric micelles	PLGA, PEG	Solvent evaporation	Drug entrapment 92%, Size 124.3 ± 6.4 nm.	2.5-2.7-fold increment in AGL bioavailability in rat plasma.	60
			Microparticle system		
Microsphere	PLGA	Emulsion solvent evaporation	Drug entrapment 75.79 ± 3.02%, Drug loading 47.06 ± 2.18%	High sustained plasma concentration up to one week with 40 folds improved in mean retention time as compared to pure AGL solution.	61
			Cyclodextrin complex		
AGL-Hydroxypropyl-β cyclodextrin (HP-β-CD) complex	Hydroxypropyl-β-cyclodextrin	Solvent evaporation	------	1.6-fold increment in AUC as compared to plain AGL	62
			Emulsion		
AGL-loaded nanoemulsion	Water, Ethanol, α-tocopherol, and Cremophor- EL	Emulsification	Droplet size 122 ± 11 nm, viscosity 28 centipoise	AGL activity was 8.21 and 1.40 times higher than the values obtained with AGL suspension and AGL ethanol solution respectively. The relative bioavailability of 594.3% compared with an AGL suspension.	63

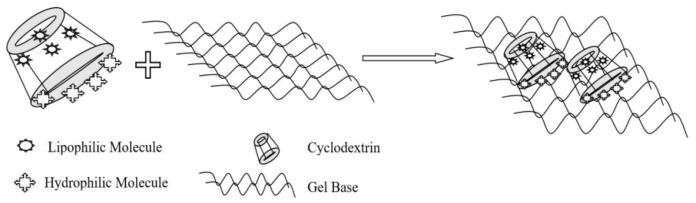

Figure 4: Cyclodextrin based nanocarriers.

and biocompatible. Chemically they are made up of glucopyranose units. Specific truncate shapes appear due to chair conformation of glucopyranose unit shown in Figure 4. Improvement in the therapeutic efficacy of curcumin was found to be improved when delivered from the cyclodextrin-based liposome.[28] Increase retention time of doxorubicin in tumor cells when administered lipid carrier along with cyclodextrin.[29] The therapeutic efficacy of camptothecin nanosponge is increased when it combined with cyclodextrin.[30]

A novel system prepared by the combination of Cyclodextrin with nanocarrier has acted as potential nanocarriers.[31] Nanosponges are polymeric Cyclodextrin inclusion systems mostly used for the delivery of phytoconstituent like Camptothecin, Paclitaxel, Quercetin, Curcumin, and Andrographolide. As a result of cross-linking of cyclodextrin unit nanoporous structure gets developed, it increases the entrapment, solubility, stability, permeation, release characteristics, and bioavailability.[32]

Loading of nanocarrier into hydrogel structure encourages the delivery of lipophilic materials.[33,34] Pushpalatha *et al.* 2019 reported that transdermal co-delivery of Curcumin (CUR) and Resveratrol (RES) using Cyclodextrin nanosponge-based hydrogel and studied for synergism against breast cancer cells. Gidwani *et al.* 2015 exhibited that a combination of Cyclodextrin and nanotechnology improves the aqueous solubility of chemotherapeutic agents.

Chitosan-hyaluronic based lipid carrier nanocomposite sponges (CHNS)

In another dual or combination approach nanostructured lipid carrier was developed by solvent diffusion method further incorporated into the chitosan-hyaluronic acid gel and lyophilized to make nanocomposite sponges[35] shown in Figure 5. Chitosan is a linear polysaccharide made up of D-Glucosamine and N-acetyl D-glucosamine. It is a biodegradable polymer that is the most commonly used polymer in drug delivery systems. The application of chitosan in the field of surgical dressing and wound healing is presumable by its mucoadhesive and homeostatic properties.[36] However, the brittleness of polymer is the major concern in formulating surgical dressing materials, which could be rectified by the incorporation of other polymers such as hyaluronic acid (HA).[37]

Hyaluronic acid is a derived polysaccharide and has a humectant property that encourages wound healing by preventing dryness of tissue. Besides, it stimulates collagen secretion at the injured tissue by the proliferation of fibroblast as a result optimistic observed on scarless wound healing.[38] Therefore, a combination approach CHNS can overcome the aforementioned hurdle. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLCs) have selective skin permeability and localization but still, responses are limited due to their inadequate rheological behavior. Therefore, the implementation of a combination approach (CHNS) by the incorporation of nanocarrier in secondary vehicles. The developed CHNS system elaborates its application and benefits. The dual approach enhances the consistency of final formulations and promotes the long-term stability of the incorporated nanocarriers.[39]

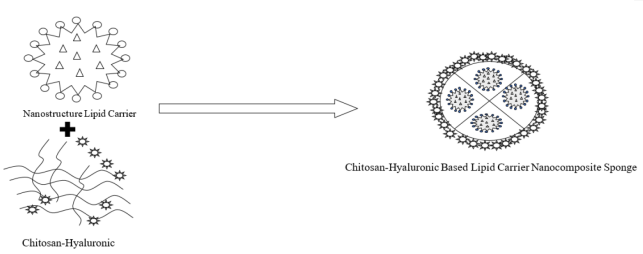

Figure 5: Chitosan-Hyaluronic based lipid carrier nanocomposite sponges.

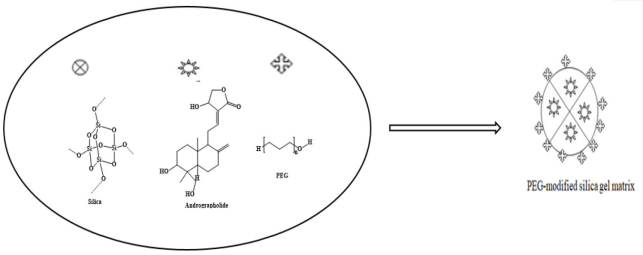

Figure 6: Andrographolide loaded PEG-modified silica gel matrix.
PEG; Polyethylene Glycol

PEG-modified silica gel matrix

Some other dual approaches were also reported by the researchers to design a controlled release formulation of AGL, in this approach the efficacy of the formulation was improved by preparing a PEG-modified silica matrix.[40] Figure 6. Like other approaches, this dual approach is also significant to design an extended drug delivery system for AGL. The amorphous and porous characteristic of silica provides better entrapment, prolongs residence time, and enhances the therapeutic effect of the drug.[41] The use of porous and nonporous silica may affect drug loading capacity, porous silica has a major prevalence over non-porous because porous silica has a greater surface area for drug loading.[42] Drug release can be regulated by the pore size of the silica; it can be controlled by using organic additives like polyethylene glycol (PEG).[43] Chakraborty *et al.*[44] reported almost 80% release of AGL accompanied with the highest burst release was obtained exclusively the highest concentration of PEG (12 % w/w) in silica. The bioavailability of AGL was found 168 hr in silica carrier while in the case of crude material it was observed nil after 7 hr. Kinetic results reveal the initial 6 hr release was rapid and subsequent slow release in the following stage (up to 168 hr). The releasing pattern of AGL was observed rapidly from the Superficially layer at the first phase and slow-release in the second phase from the inner pore of the silica matrix. A three-dimensional network of silica immobilized AGL effectively controlled the release rate of the drug.[45]

PLGA nanoparticle embedded into the gelatin-based hydrogel

Another dual approach is based on the formulation of AGL-PLGA nanocarriers incorporated in gelatin-based hydrogel (GBH) to design an extended drug delivery system. AGL-PLGA nanoparticles were prepared by emulsion solvent evaporation method and embedded into the gelatin-based hydrogel Figure 7. The terminal ester group present in PLGA shows a significant role in the modified release behavior of AGL. However, the combination approach of GBH with AGL-PLGA nanoparticles prolongs the release of AGL for more than 1 month. The combination carriers of PLGA and GBH significantly impact the release pattern of AGL.

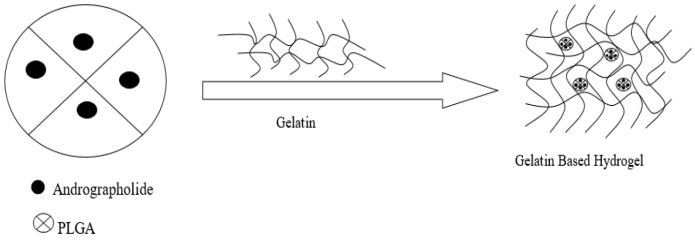

Figure 7: PLGA nanoparticle embedded into the gelatin-based hydrogel. PLGA; Poly D, L-lactide-co-glycolic acid

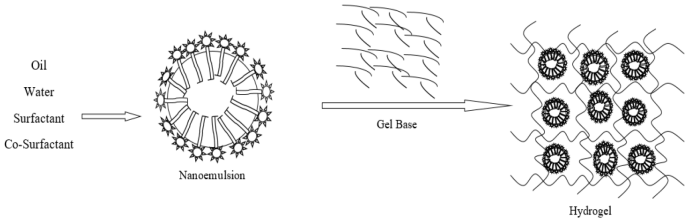

Figure 8: Nanoemulsion-based hydrogel.

Modified release pattern observed due to the difference in hydrophilicity of terminal end group. Results show that the formulation of AGL-NPs embedded into GBH has prolonged retention for almost 2 months for sheet type of hydrogel and more than 2 months for beads type of hydrogel. Therefore, a dual approach-based AGL-NPs embedded GBH is a potent formulation that could minimize the drug administration frequency and extend the duration to improve the clinical effect.[46]

Nanoemulsion-based hydrogel

Nanoemulsion can improve drug solubility and stability but has limitations for topical application. The incorporation of nanoemulsion into a hydrogel increases the viscosity of the system which can prolong the drug residence time[47] Figure 8.

Nanoemulsion is composed of oil, water, surfactant, and co-surfactant.[48] The Characteristics features of nanoemulsion are stability, solubility, and bioavailability. However, nanoemulsion is confined in terms of viscosity that limited their topical application.[49] This limitation can be overcome by incorporating nanoemulsion into a hydrogel. The formation of hydrogel imparts significant viscosity and prolong drug residence time.[50] Carbopol was employed as the gelling agent, whereas other excipients are propylene glycol, oleic acid, triethanolamine, methylparaben, and propylparaben were also added to produce hydrogel base.

CONCLUSION

AGL has a broad range of therapeutic potential but their clinical response is restricted due to their poor aqueous solubility, stability in oral administration, and low bioavailability. Various modern approaches were made to improve the limitation associated with AGL. Based on previous research it was concluded dual approach or combination of nanocarrier systems efficiently overcome the hurdle associated with AGL delivery and potentiate its clinical response, a similar approach can be made for the other kind of phytoconstituent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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