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Current nanocarriers in therapeutic improvement of Andrographolide

Van Hong Nguyen*, An Hong Nguyen Pham

Pharmaceutical Engineering Lab, School of Biomedical Engineering, International University, Vietnam National University, Ho Chi Minh city

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Abstract:

Currently, herbs have been investigated for novel bioactivities and improvement of traditional therapeutic effectiveness. Among them, *Andrographis paniculata*, with the active component Andrographolide, is well recognized as an anti-inflammatory, anti-bacterial, anti-cancer, anti-hypertensive, anti-hyperglycaemic, hepatoprotective, and anti-hyperlipidaemic compound. However, Andrographolide has poor physicochemical properties that limit its medical application. In this review article, nano drug delivery systems including nanovesicles, inorganic nanoparticles, lipid-based nanoparticles, polymeric nanoparticles, nanocrystals, nanoemulsions, and microemulsions, which can deliver Andrographolide through different routes such as oral, injection, or dermal, and their influences in increasing treatment benefits are presented.

Keywords: ***A. paniculata*, Andrographolide, herbal, nanocarriers, therapeutic effect.**

Classification number: **3.6**

Introduction

In the discovery of novel drugs, natural compounds have impressive properties and characteristics such as better therapeutic effects as well as low toxicity compared to synthesized agents. Andrographolide (AG) is the representative bioactive chemical of the plant *Andrographis paniculata* that is currently being explored in the pharmaceutical industry. This compound proposes significant beneficial advantages such as antibacterial [1], anti-inflammation, cancer prevention, and neuroprotective properties (see Fig. 1) [2]. Antimicrobial activity is the most prominent effect, which has been applied to the treatment of infectious diseases since ancient times, for example, for gastrointestinal inflammation-related diseases and respiratory infection [3]. Also, AG can be considered as an antiviral agent [4], especially express inhibition of SARS-CoV-2 in Calu-3, which are human lung epithelial cells [5]. Promising treatments of AG could be confirmed by numerous current clinical trials on lung infection, arthritis, rheumatoid, gastrointestinal cancer, migraine, cognitive impairment, COVID-19 virus, and so on.

AG is a white crystalline powder with an extremely bitter flavour. At neutral to basic pH, Andrographolide is unstable and hydrolyses to an inert product. The high hydrophobicity (log P=2.632±0.135), poor water solubility (3.29±0.73 mg/ml), and fast transportation by P-glycoprotein out of the cells are all factors that contribute to the poor bioavailability of AG. Therefore, it is important to study methodologies to improve therapeutic treatment with AG. Many pharmaceutical techniques such as solid dispersion [6], inclusion complex [7], and nanotechnology [8] have been investigated to improve the solubility and permeability of AG.

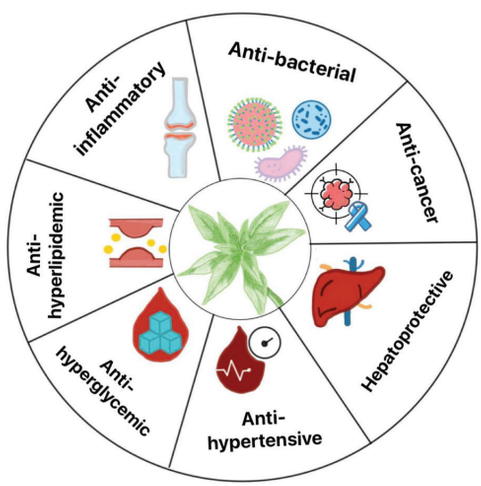

Fig. 1. Therapeutic effects of Andrographolide.

Nanotechnology is considered the most promising strategy for drug delivery systems, especially for natural compounds and specifically for AG [9]. The incorporation of natural herbs in nanoplatforms is necessary for the enhancement of biocompatibility, the prolongation of drug circulation in living bodies, and the ease of permeability through the cell membrane for effective treatments. In particular, AG nano formulations show better results in bioavailability, targeting effect, and safety [10]. Hence, modern drug delivery systems loading AG through various uptake routes, which could improve solubility, stability, absorption, and overcome resistance mechanisms in tumour cells are summarized.

*Corresponding author: Email: nhvan@hcmiu.edu.vn

Nano drug delivery systems loading Andrographolide

Nanostructures including inorganic nanoparticles (NPs), polymeric NPs, lipid-based NPs, micelles, and nanovesicles are employed for delivery of AG to boost the therapeutic effects on various types of diseases.

Inorganic NPs

Inorganic NPs are non-toxic, biocompatible, as well as hydrophilic and highly stable in comparison with organic ones [11]. Besides, inorganic NPs have received a lot of attention as drug or gene delivery vehicles because of their high cellular absorption ability, low immunogenic response, and low cytotoxicity. Inorganic NPs include calcium phosphate, silica, iron oxide, magnesium phosphate, gold, and other metals. The electromagnetic, optical, and catalytic properties of metal NPs such as gold and silver NPs are known to be influenced by their shape and size. The targetability and controlled release of these NPs were obtained through physicochemical modification [8] mainly by conjugating with organic components, making them exceedingly biocompatible. The combination of inorganic NP design with multidisciplinary approaches enables future applications of AG in drug delivery and tissue engineering [11].

Mesoporous silica NPs (MSNs) have a highly organized mesoporous structure that may give an exceptionally high specific surface area and aperture volume, which are suited for drug loading among different inorganic NPs, especially AG. Therefore, AG powder was loaded onto MSNs, obtained size around 100 nm, with a significantly high loading capacity (LC) of 22.38±0.71%. Furthermore, *in vitro* evaluation proved that AG MSNs could decrease post-inflammatory factors by about 40%. Moreover, AG-loaded-MSNs were designed as a pH-responsive system, which enable these NPs to break down in an acidic osteoarthritis environment. With a phospholipid coating layer, MSNs as nanocarriers demonstrated good lubricating capability in the treatment of osteoarthritis [8] (Table 1).

Polymeric NPs

Polymeric NPs are one of the most popular types of nanocarriers, which contain natural polymers like chitosan, alginate, gelatine, and synthesis polymers such as polylactide (PLA) [21] and copolymers like polylactide-co-glycolide (PLGA) [22]. Synthetic polymers with high batch-to-batch repeatability and purity make it easier to change the pattern of drug release from polymeric NPs [23].

In one study, a cationic-modified PLGA was used to fabricate biopolymeric NPs loading *A. paniculata* extraction in 95% ethanol. Briefly, the preparation of the NPs is conducted with PLGA, Pluronic F-127, and chloroform, then collected by ultracentrifugation. AG NPs had an encapsulation efficiency (EE) value of 43.39±0.33% in a 200-nm size range. The AG polymeric NPs had an important impact on the induction of CCl_4 activity by the increase of antioxidant enzymes in the liver at more than 50% effectiveness compared to the blank AG ones [15]. Besides,

Table 1. Andrographolide nanoparticle excipients.

Nano-types	Excipients	Size (nm)	PDI	Zeta potential (mV)	EE (%)	LC (%)	Reference
Vesicles	**Liposomes:** Soybean lecithin Cholesterol Mannitol	77.91±22.91	0.22±0.04	-56.13±3.33	94.77±1.77	6.70±0.69	[12]
	Niosomes: Span 60 Cholesterol Caprylocaproyl macrogol-8 glycerides	125-226	<0.1	-34.02±1.40	97.75±1.28	N/A	[13, 14]
Inorganic NPs	Cetyltrimethyl ammonium bromide (CTAB) 2-ethoxyethanol Aqueous ammonia Tetraethyl orthosilicate (TEOS)	100	<0.1	−20.93±3.40	43.39±0.33	22.38±0.71	[8]
Polymeric NPs	PLGA Chitosan Pluronic F-127	229.7±17.17	0.234±0.02	34.4±1.87	43.39±0.33	N/A	[15]
SLNs	Egg lecithin Tween-80 Anhydrous alcohol Glyceryl-monostearate Compritol ATO888 Mannitol	286.1±8.03	0.3±0.03	−20.5±0.3	91.00±0.09	3.49±0.03	[16]
Nano-emulsion	Coconut oil Sesame oil Jojoba oil Polysorbate 80 Sorbitan oleate 80 Propylene glycol	225.2±3.2	0.59±0.02	-8.52±2.14	93.76±0.03	0.27±0.00	[17, 18]
Micro-emulsion	Tween 80 Isopropyl myristate Glycerol Sorbitol Arachis oil Soybean oil	15.9-18.6	0.173	22.90±31.01	N/A	N/A	[19]
Micelles	NH_2-PEG-NH_2 polymer PLGA-COOH Dicyclohexyl-carbodimide N-hydroxysuccinimide	80	<0.18	-3.5	92.1±0.98	8.4±0.04	[20]

chitosan-modified AG NPs on hepatic antioxidant enzymes were also fabricated to enhance the bioactivities of AG [24]. Poorly soluble chemicals may have significant adverse effects when systemically given over long periods of time. Incorporation of medicinal compounds in the hydrophobic cavity of NPs produces the desired outcomes *in vitro* and *in vivo*. Furthermore, the procedures for synthesizing polymers, which can have a variety of side effects and toxicity when using chemical methods, should be considered [25].

Micelles

Polymeric micelles, which are generated by the self-assembly of amphiphilic blocks or grafted copolymers, have the following advantages such as suitability for delivery of both hydrophilic and hydrophobic bioactive chemicals, biodegradability, biocompatibility, and an extended lifecycle *in vivo* through a "stealth effect", which allows them to be more precise in active drug targeting [26].

In recent years, numerous types of copolymers have been developed. Because of their biocompatibility and biodegradability, as well as their ability to control drug release, amphiphilic copolymers of PEG and PLGA are mainly used for polymeric micelle formation. In *in vitro* cytotoxicity experiments on MAD-MB-231 cells, even at high concentrations, blank PLGA-PEG-PLGA micelles exhibited no cytotoxicity. Besides, AG polymeric micelles by modified PLGA-PEG-PLGA copolymers had sufficient size, less than 200 nm with no aggregation or adhesion, as well as EE and loading capacity (LC) values of 92.1±0.98%, 8.4±0.04%, respectively. There was no significant change in

size or zeta-potential after 15-day storage of AG micelles. When compared to free AG formulations, the proportion of apoptotic cells produced by AG micelles was substantially greater. Based on all of these results, such as the cytotoxicity, cell cycle block, and cell apoptosis assays, it was found that AG-loaded micelles had a stronger effect on MAD-MB-231 cells [20] (Fig. 2).

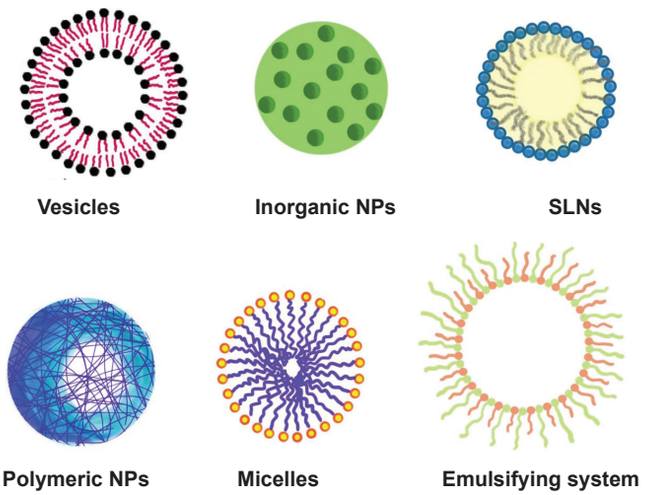

Fig. 2. Classification of Andrographolide NPs.

Nanovesicles

Liposomes

Liposomes are phospholipid bilayer nanovesicles specifically designed for advanced permeability through cell membranes [27]. Additionally, other benefits of liposomes are extreme biocompatibility, non-toxicity, and practicality to the human body, especially for injection route. However, liposomes have low stability in liquid form, and are prone to drug leakage due to the lipophilic layer being easily absorbed through membrane, gut wall of the GI tract, or the hydrophilic compound being dissolved in the blood flow [28].

Liposomes encapsulating AG were developed as multilayer-multilamellar structures with phosphatidylethanolamine, cholesterol, and diacetyl phosphate [29]. In one study, AG powder was loaded into a liposomal system of small size (approximately 78 nm) and produced a high encapsulation efficiency value of 94%. AG liposomes were prepared with the injection method and then freeze-dried to obtain liposomal AG dry powder inhalers (LADPIs). AG liposomes were small and stable with a mean size of 77.91 nm and zeta potential of -56.13 mV, high encapsulation efficiency (EE) of 94.77±1.77% and drug loading (DL) of 6.70±0.69%. Liposomes were well recovered after re-hydration of LADPIs and were suitable for pulmonary delivery [12]. In another study, the characterization determined that the EE and LC of AG in liposomes were 79.03±6.23% and 2.91±0.09%, respectively. The EE value of these AG liposomes were not as high as the previous liposomes for lungs as there was other lipids in the formulation that would affect the encapsulation [30].

Niosomes

Niosomes are bilayer vesicles made of non-ionic surfactants with amphiphilic substances that increase drug loading. As opposed to liposomes, niosomes are extremely stable, require no refrigeration, and have a moderate production cost. Niosomes enable loading of both hydrophilic and hydrophobic agents, which enhance the solubility and mobility of weakly water soluble pharmaceutical agents through phospholipid layers. Moreover, niosomes can modify membrane permeability, osmosis absorption, and biocompatibility of bioactives resulting in better therapeutic effectiveness [31].

AG-loaded niosomes were fabricated for wound healing applications. Previously, AG was extracted using water and ethanol as solvents. Then, that extraction was loaded into a niosome formulation first, and then mixed into a Carbopol gel at a suitable concentration. Among various types of NPs, AG niosomes seem to have the highest EE value at 97.75±1.28% with water extract and 97.21±1.89% with 70% ethanol extract. Moreover, AG niosomes also had a good size range of 125-226 nm. AG niosomal gel enhanced the viability of human skin fibroblast cells, and recovered 100% wound healing closure on rats [13].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are being developed into colloidal carriers, which are a composition of lipid ingredients and water-soluble surfactants. SLNs shield active ingredients from oxidation by encapsulating them and delivering a controlled release of a drug over time. Moreover, SLN preparation methods are simple and avoid the need for harmful solvents. Additionally, the adherence of SLNs to the gut wall and the absorption enhancing impact of lipids on pharmacological activities were mostly responsible for the absorption enhancing effect of orally administered SLNs [32].

AG-SLNs were prepared by high pressure homogenization using Compritol 888 ATO and glyceryl monostearate (GMS) as lipid carriers and lecithin and Tween-80 as surfactants. The resulting SLN morphology was spherical or oval, and no drug crystals occurred. AG-SLNs had an EE value of 91.00±0.09% and DL value of 3.49±0.03%. Transformation of AG-SLNs into solid form by lyophilization with mannitol without changes in size range or morphology. AG-SLNs enhanced AG bioavailability, about 2.41 times greater than the AG suspension, as well as antihyperlipidemic efficacy by enhancing AG solubility, stability in the gut, and altering AG transport mode in Caco-2 cells. Lipid-lowering effects of AG were obviously boosted by SLN, suggesting that AG-SLNs might improve AG oral absorption and therefore improve the lipid-lowering impact [16].

In another study, AG-SLNs were fabricated for the transportation of drugs through the blood brain barrier by emulsion [33]. Briefly, Compritol 888 ATO and Brij 78 were dissolved in solvents with various ratios of AG (2.5, 5 and 10%),

which was then added dropwise to PBS at pH 7.4 under magnetic stirring. The highest EE and LC percentages of AG-SLNs at this level were 92.4±1.77% and 8.4±0.16%, respectively. AG-SLNs in drying powder or suspension form are stable for 30 days at 4°C and 25°C, respectively. The results of *in vivo* experiments demonstrated that AG-SLNs could cross the blood-brain barrier and reach brain tissues, hence boosting AG penetration. From the great characteristics of this development, SLNs are potential systems to improve the treatment of neurodegenerative illnesses of AG.

Micro-emulsions

Microemulsions appear as transparent solutions with particle sizes less than 100 nm and are physically stable under thermodynamic conditions by using a high concentration of surfactants. In one study, the formulation of AG microemulsions contained an oil phase with isopropyl myristate, arachis oil, and soybean oil. The co-surfactants were absolute alcohol, glycerol, and sorbitol, and the aqueous phase was bi-distilled water. Tween 80 was chosen as the primary surfactant due to its low cytotoxicity and stability across pH and ionic strength ranges. In this design, with the amount (w/w) of surfactant Tween 80 at 25%, the oil phase at 2.5%, and alcohol at 50%, the optimized oil-in-water microemulsion had a size of nearly 16 nm. Furthermore, the AG microemulsion has low oral toxicity, as demonstrated by the rat study [19]. In another study, AG in ethanolic extract was loaded in a microemulsion prepared by cholesterol and isopropyl myristate as the oil phase, bile salts, lecithin as a surfactant, and RH-40 and ethanol as co-surfactants. The resulting microemulsion had a size above 19 nm, and an improved bioavailability of AG over 6 times greater than pure ethanolic extract on rabbits [34].

Nanoemulsions

Nanoemulsions are submicron-sized colloidal particle systems with diameter ranges between 10 and 1,000 nm. Oil-in-water AG-loaded nanoemulsions (AG-NE) were made to improve AG effectiveness for skin treatment. In the study, AG-NE had a reasonable EE of 93.76±0.03%. However, the LC was only 0.27±0.00%. A combination of Tween 80 and Span 80 was used as an emulsifier with a ratio of 5:1 at 10% w/w. AG and AG-NE were tested for cytotoxicity in two types of cells, which are non-melanoma skin cancer cells (A-431 cells) and normal skin fibroblast cells (HFF-1 cells) at concentrations of 30-100 µg/ml. Both the NE base and AG-NE had nanometre-sized droplets, were able to resist the effect of centrifugal force. With the formulation of the nanoemulsion, the bioavailability of AG for oral route was enhanced by about 8 times more than AG suspension [18]. For the further investigation of leishmaniasis treatment, and especially for the intraperitoneal injection, nano systems of emulsions for AG were prepared using a solvent evaporation technique to evaluate the different ratios between the infection proportions of treated and untreated macrophages. Moreover, they used vitamin E as the stabilizer for the protection of the drugs and enhancement of the permeability through cell membranes [35]. Over the course of 3 months, the size of this AG-NE did not significantly change, and the quantity of loaded AG remained the same [36] (Table 2).

Table 2. Route administration of Andrographolide nanocarriers.

Route	AG bioactivities	Bioactivity	Reference
Pulmonary delivery	Liposomal AG dry powder to cure of *S. aureus*-induced pneumonia.	Antibacterial	[12]
Oral treatment	In diabetic rats without insulin, increasing glucose consumption lowers plasma glucose.	Anti-hyperglycaemic	[37]
	Reduces plasma glucose levels and increases β-endorphin as the immunoreactivity.		[38]
	Lower blood glucose and preserve pancreatic beta cells at the same time.		[39]
	Decrease the levels of serum creatinine, serum urea nitrogen, urinary albumin excretion, serum urea, and blood glucose in induced diabetic rats.		[40]
Gavage-force feeding route	The extraction of AG protects against 5 myocardial damages in high fat diet-induced obese mice models.	Anti-hypertensive	[41]
Intragastric administration	The bioavailability and antihyperlipidemic activity were improved by AG-SLNs by increasing the solubility and stability of AG in the intestine and by changing its transport mode in Caco-2 cell.	Anti-hyperlipidaemic	[16]
	AG exhibited a significant inhibition on the mouse model by lowering macrophage inflammatory protein (MIP-2) mRNA.	Anti-inflammation	[42]
Intraperitoneally	Against oxidative stress-induced liver damage.	Hepatoprotective	[15]
	Inhibits NF-κB and MAPK-mediated inflammatory responses.	Anti-inflammation	[43]
-	Inhibits gastric cancer cell proliferation and metastasis of the gastric cell line SGC7901.	Anticancer	[44]
	Enhances the expression pattern of proapoptotic proteins like caspase-3 and caspase-9, which suggest the involvement of the mitochondrial apoptotic pathway in the chemo preventive effect.	Anticancer	[45]
	Induced cell cycle arrest and apoptotic death in MDA-MB-231 breast cancer cells without affecting growth of normal cell.	Anticancer	[46]

Therapeutic effects of Andrographolide

Anti-bacterial

The antibacterial bioactivity of AG is related to reduction of pathogens and regulation of the immune system to inhibit inflammatory actions. AG is considered as a potential inhibitor of NF-kB, which is one of the specific antibacterial responses [47]. Early attempts to treat arthritis and leishmaniasis with AG and synthesized prodrugs failed due to solubility and distribution issues. In previous studies, the AG-β-cyclodextrin inclusion complex performed effective treatment against *S. aureus* pneumonia [48]. Since the discovery of its antiviral and antibacterial properties, AG was delivered by nanocarrier in the treatment of parasitic diseases [49]. In the *in vivo* test of hamster models, AG liposomes decorated with macrophage mannosyl-fucosyl receptors showed potential treatment of the leishmaniasis infection as well as better safety on liver and kidney in hamster models [29]. In another study, AG liposomes reduced the bacterial activity, lessened lung injury, and inhibited the inflammatory reactions caused by bacterial pneumonia. Noticeably, AG liposomal in inhaler powder form expressed higher anti-*S. aureus* lung effects *in vivo* than a ten-fold

dose of AG, as well as penicillin. Hence, AG has the ability to regulate the immune response in order to maintain the antibacterial effect while inhibiting the inflammatory response [12].

Anti-inflammatory

AG may affect inflammatory responses related glycolysis, which can suppress inflammation and cancer growth [50]. Hypoxia, anaerobic glycolysis, and lactification occur due to the increase of cell metabolic activity in the inflammatory state. A pH-responsive, mesoporous, silica-loaded AG, coated with phospholipid to enhance lubricant ability for local treatment of osteoarthritis has been proposed. The improvement of AG effectiveness on osteoarthritis by this nanocarrier was confirmed by IL-1-induced tissue in a rat model [8]. AG was also loaded into niosomes, followed by incorporating gel to enhance the treatment of the wound. Macroscopic assessments were conducted in the initial wound areas to compare the AG-loaded niosomal gel and blank gel. The AG niosomal gel showed less inflammation and less scarring within 3 days. From day 7 to day 10 of the experiment, the rat wound had no irritation or red spots on the skin and its hair rapidly regrew under the treatment of AG niosomal gel. The anti-inflammatory and anti-oxidant properties of AG could eliminate oxidative stress molecules, boost wound closure, leading to improve the vascular channel generation and the epithelial cell proliferation [51]. The anti-inflammatory impact of AG was significantly increased by microemulsions, which were shown to have two-fold greater bioavailability than AG tablets [19].

Anti-hyperglycemic

AG has been proven for the treatment of high glucose in blood by reducing levels of glucose and albumin while preserving pancreatic beta cells and increasing beta-endorphins as immunoreactivity [40]. AG was placed in a nano-emulsion and nano-suspension with Tween 20, PEG 400, and Capryol 90 in a specific ratio [10]. The results indicated a significant decrease in blood glucose levels in rat models within 8 days when treated with AG nano-emulsion and nano-suspension [52]. From the *in vitro* tests of pancreatic beta cells, these AG nano-emulsions and suspensions showed the capability of insulin secretion by immunoreactive analysis as well as high biocompatibility and bioavailability [53].

Anti-hypertensive

A. paniculata extraction protected mice from myocardial damage in high fat diet mice models, which indicated AG's effects of reducing blood pressure and treatment of cardiac hypertrophy [54]. Besides, AG could decrease air proinflammatory cell adhesion, lung irritation, lung damage, as well as lower the levels of protein and mRNA in the cytokine serum and bronchoalveolar fluid [43]. Additionally, AG was promoted for the enhancement of therapeutic effects in the treatment of pulmonary hypertension by oral route in mouse models based on the results of decreasing oxidative stress and the pathways of inflammatory cells [55].

Anti-hyperlipidemic

AG and *A. paniculata* are well known for their antidiabetic and antihyperlipidemic effects [56]. In comparison with AG suspensions, the SLNs show better bioavailability by increasing the solubility and stability of AG in the intestines [16], which strengthen proof of antihyperlipidemic effects of AG [30]. Specifically, SLNs sustained the release of AG for up to 24 h compared to 8 h for AG solution *in vitro*, and bioavailability increased by about 2.5 times *in vivo*. Furthermore, the key mechanisms for increased AG-SLNs bioavailability were clarified including an increase in solubility, a reduction in intestinal tract metabolism (particularly in the duodenum), improved colon absorption, and a change in transport mode. AG lipid-lowering action is boosted by AG-SLNs, suggesting that they are a potential cargo for AG via oral uptake [16].

Hepatoprotective

Antiviral medicines, steroids, and vaccinations are especially harmful to the liver when used in long-term treatments like antitubercular, antiretroviral, or anticancer chemotherapy. AG pre-treatment considerably protected the liver from the reduction of the quantity and quality of bile caused by paracetamol. In conscious rats and anesthetized guinea pigs, the increases in bile flow, bile salt, and bile acids reveal that AG had a significant choleretic effect that is dependent on the dosage that increases from 4.8% to 73% [57]. The studies of hepatoprotective effects of AG in rats were demonstrated by the acute hepatitis induced in them [58]. Liver-protective effect of *A. paniculata* was improved by polymeric micelles, which were formed by modified poly(lactic-co-glycolic) NPs in CCl_4 acute liver injury models [15]. Chitosan-modified AGNPs increased AG activity on hepatic antioxidant enzymes [24]. Furthermore, chitosan AGNPs were shown to protect the liver against mitochondrial liver damage. Many other factors have been linked to increased hepatoprotection including the overexpression of various antioxidative enzymes and the replenishment of glutathione in the liver. Cytokine modulation by chitosan AGNPs improved CCl_4-damaged liver architecture recovery. As a result, newly designed AG polymeric NPs broadened the treatment of oxidative stress and hepatocellular inflammation. To allow entry into clinical trials, more pharmacokinetic studies of similarly designed nanosystems are needed, and one is currently underway [15].

Anti-cancer

In cancer cells, AG produces cell cycle apoptosis without affecting other healthy cell growth [59]. PLGA-PEG-PLGA micelles increased cellular uptake of AG by more than twofold, resulting in significantly higher toxicity on breast cancer MAD-MB-231 cells *in vitro* and nearly threefold AUC in rats [20]. AG liposomes were prepared to treat breast cancer cells and subjected to wound healing and trans-well experiments. In wound healing experiments, liposome-loaded AG showed a significantly lower migratory capacity of 4T1 cells than the other groups. In the trans-well experiment, for the loaded liposome group, a comparable reduction of breast cancer cell invasion was consistently seen [30].

Future perspective

AG poses a significantly large number of good advantages in disease treatments, especially proved by human trials. However, low solubility and stability may be a barrier to pharmaceutical product design along with the hard, bitter flavour that is an additional complication in AG formulation optimization. Therefore, there are demands for scientists to overcome those issues of AG, which is the prospective active agent for infectious illnesses, specifically for the COVID-19 pandemic. Besides, from Table 3, the exact amount of pure AG, and not only the *A. paniculata* extract, needs to be published in papers, the product label, and product description for a better understanding and the correct use of AG by consumers. Nanotechnology has been shedding light on the widening and realistic application of AG. Promising products containing AG will go to the market earlier with a tremendous increase in calling clinical trials for various treatments such as neuroprotective, hepatoprotective, migraine, antibacterial-related diseases, anti-inflammation related diseases, COVID-19 and so on.

Table 3. Supplemental products containing Andrographolide.

Function	Product	Dosage form	Dose
Immune support	Bixa Botanical	Capsule	450 mg *A. paniculata* extract
	Maple Life Science	Capsule	400 mg *A. paniculata* extract
	Medi Herb: Andrographis complex	Tablet	100 mg *A. paniculata* extract
Liver functions support	Tefroliv Forte Tablet	Tablet	60 mg *A. paniculata* extract
	Stimuliv Syrup	Syrup	60 mg *A. paniculata* extract
Treatment of respiratory tract, skin, and intestinal infections	Regenerative Nutrition	Capsule	400 mg *A. paniculata* extract
Cough, bronchitis treatment	Traphaco: Xuyen Tam Lien	Capsule	160 mg *A. paniculata* extract
Prevent bronchitis infection	OPG: Xuyen Tam Lien nasal and throat spray	Spray	*A. paniculata* extract

Conclusions

AG possesses various therapeutic activities like liver protection, analgesic properties, anti-inflammation, as well as antihyperglycemic and anti-tumour properties. However, the harsh taste, low water solubility, considerable liver first-pass degradation, and low oral bioavailability has urges the development of AG formulations. Advancements in nano drug delivery systems have already strengthened and broadened the usage of AG through various administrations such as pulmonary delivery, oral route, skin application, and so on. Numerous nanocarriers have been prepared including inorganic NPs, polymeric NPs, micelles, nanovesicles, SLNs, and nano- and micro- emulsions, which show effectiveness in the improvement of AG's physicochemical properties as well as bioavailability *in vitro and in vivo*. However, remaining challenges include maintaining structural integrity, enhancing biofluid stability, as well as improving biocompatibility and manufacturing ease and safety while reducing adverse effects and increasing efficacy.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

[1] L. Zhang, et al. (2020), "Effect of Andrographolide and its analogs on bacterial infection: A review", *Pharmacology*, **105(3-4)**, pp.123-134.

[2] R. Hossain, et al. (2022), "Neurobiological promises of the bitter diterpene lactone Andrographolide", *Oxidative Medicine and Cellular Longevity*, DOI: 10.1155/2022/3079577.

[3] D. Wang, et al. (2021), "Andrographolide and its derivatives are effective compounds for gastrointestinal protection: A review", *European Review for Medical and Pharmacological Sciences*, **25(5)**, pp.2367-2382.

[4] R. Latif, C.Y. Wang (2020), "Andrographolide as a potent and promising antiviral agent", *Chinese Journal of Natural Medicines*, **18(10)**, pp.760-769.

[5] S. Jeon, et al. (2020), "Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs", *Antimicrobial Agents and Chemotherapy*, **64(7)**, DOI: 10.1128/AAC.00819-20.

[6] C.C. Yen, et al. (2020), "Oral bioavailability enhancement and anti-fatigue assessment of the Andrographolide loaded solid dispersion", *International Journal of Molecular Sciences*, **21(7)**, DOI: 10.3390/ijms21072506.

[7] H. Gao, et al. (2021), "Integrated computer-aided formulation design: A case study of Andrographolide/cyclodextrin ternary formulation", *Asian Journal of Pharmaceutical Sciences*, **16(4)**, pp.494-507.

[8] M. He, et al. (2021), "A pH-responsive mesoporous silica nanoparticles-based drug delivery system with controlled release of Andrographolide for OA treatment", *Regenerative Biomaterials*, **8(4)**, DOI: 10.1093/rb/rbab020.

[9] V. Dhapte, V. Pokharkar (2019), " Chapter 13 - Nanosystems for drug delivery: Design, engineering, and applications", *Green Synthesis, Characterization and Applications of Nanoparticles*, Elsevier, pp.321-345.

[10] Y. Syukri, et al. (2018), "Novel self-nano emulsifying drug delivery system (SNEDDS) of Andrographolide isolated from *Andrographis paniculata* nees: Characterization, in-vitro and in-vivo assessment", *Journal of Drug Delivery Science and Technology*, **47**, pp.514-520.

[11] W. Paul, C.P. Sharma (2020), "Inorganic nanoparticles for targeted drug delivery", *Biointegration of Medical Implant Materials*, pp.333-373.

[12] M. Li, et al. (2017), "Liposomal Andrographolide dry powder inhalers for treatment of bacterial pneumonia via anti-inflammatory pathway", *International Journal of Pharmaceutics*, **528(1-2)**, pp.163-171.

[13] R. Jamaludin, et al. (2021), "Andrographis paniculata-loaded niosome for wound healing application: Characterisation and *in vivo* analyses", *Journal of Drug Delivery Science and Technology*, **63**, DOI: 10.1016/j.jddst.2021.102427.

[14] F. Nowroozi, et al. (2018), "Effect of surfactant type, cholesterol content and various downsizing methods on the particle size of niosomes", *Iranian Journal of Pharmaceutical Research*, **17(Suppl.2)**, pp.1-11.

[15] P. Roy, et al. (2014), "Engineered Andrographolide nanosystems for smart recovery in hepatotoxic conditions", *International Journal of Nanomedicine*, **9**, pp.4723-4735.

[16] T. Yang, et al. (2013), "Preparation of Andrographolide-loaded solid lipid nanoparticles and their *in vitro* and *in vivo* evaluations: Characteristics, release, absorption, transports, pharmacokinetics, and antihyperlipidemic activity", *Journal of Pharmaceutical Sciences*, **102(12)**, pp.4414-4425.

[17] N. Sooksai, et al. (2019), "Andrographolide-loaded nanoemulsion and its activity against non-melanoma skin cancer cells", *Key Engineering Materials*, **819**, pp.139-144.

[18] C.C. Yen, et al. (2018), "Nanoemulsion as a strategy for improving the oral bioavailability and anti-inflammatory activity of Andrographolide", *International Journal of Nanomedicine*, **13**, pp. 669-680.

[19] H. Du, et al. (2012), "Preparation and evaluation of Andrographolide-loaded microemulsion", *Journal of Microencapsulation*, **29(7)**, pp.657-665.

[20] J. Zhang, et al. (2014), "Andrographolide-loaded PLGA-PEG-PLGA micelles to improve its bioavailability and anticancer efficacy", *Expert Opinion on Drug Delivery*, **11(9)**, pp.1367-1380.

[21] O. Escalona-Rayo, et al. (2019), "Rapamycin-loaded polysorbate 80-coated PLGA nanoparticles: Optimization of formulation variables and *in vitro* anti-glioma assessment", *Journal of Drug Delivery Science and Technology*, **52**, pp.488-499.

[22] M. Szczęch, K. Szczepanowicz (2020), "Polymeric core-shell nanoparticles prepared by spontaneous emulsification solvent evaporation and functionalized by the layer-by-layer method", *Nanomaterials*, **10(3)**, DOI: 10.3390/nano10030496.

[23] I. Khan, K. Saeed, I. Khan (2019), "Nanoparticles: Properties, applications and toxicities", *Arabian Journal of Chemistry*, **12(7)**, pp.908-931.

[24] A. Makhlof, , Y. Tozuka, H. Takeuchi (2011), "Design and evaluation of novel pH-sensitive chitosan nanoparticles for oral insulin delivery", *European Journal of Pharmaceutical Sciences*, **42(5)**, pp.445-451.

[25] A. Kahru, H.C. Dubourguier (2010), "From ecotoxicology to nanoecotoxicology", *Toxicology*, **269(2-3)**, pp.105-119.

[26] M.C.I.M. Amin, et al. (2017), "Polymeric micelles for drug targeting and delivery", *Nanotechnology-Based Approaches for Targeting and Delivery of Drugs and Genes*, Elsevier, pp.167-202.

[27] S.K. Sahoo, V. Labhasetwar (2003), "Nanotech approaches to drug delivery and imaging", *Drug Discovery Today*, **8(24)**, pp.1112-1120.

[28] A. Gabizon, et al. (1998), "Development of liposomal anthracyclines: From basics to clinical applications", *Journal of Controlled Release*, **53(1-3)**, pp.275-279.

[29] J. Sinha, et al. (2000), "Targeting of liposomal Andrographolide to L. donovani - infected macrophages *in vivo*", *Drug Delivery*, **7(4)**, pp.209-213.

[30] X. Kang, et al. (2018), "Liposomal codelivery of doxorubicin and Andrographolide inhibits breast cancer growth and metastasis", *Molecular Pharmaceutics*, **15(4)**, pp.1618-1626.

[31] R. Khan, R. Irchhaiya (2016), "Niosomes: A potential tool for novel drug delivery", *Journal of Pharmaceutical Investigation*, **46(3)**, pp.195-204.

[32] E. Salah, et al. (2020), "Solid lipid nanoparticles for enhanced oral absorption: A review", *Colloids and Surfaces B: Biointerfaces*, **196**, DOI: 10.1016/j.colsurfb.2020.111305.

[33] G. Graverini, et al. (2018), "Solid lipid nanoparticles for delivery of Andrographolide across the blood-brain barrier: *in vitro* and *in vivo* evaluation", *Colloids and Surfaces B: Biointerfaces*, **161**, pp.302-313.

[34] L. Xiao-Yan, et al. (2016), "A new biocompatible microemulsion increases extraction yield and bioavailability of Andrographis paniculata", *Chinese Journal of Natural Medicines*, **14(9)**, pp.683-691.

[35] S. Mondal, et al. (2013), "*In vitro* susceptibilities of wild and drug resistant leishmania donovani amastigote stages to Andrographolide nanoparticle: Role of vitamin E derivative TPGS for nanoparticle efficacy", *PLOS One*, **8(12)**, DOI: 10.1371/journal.pone.0081492.

[36] P. Roy, et al. (2013), "Engineered Andrographolide nanoparticles mitigate paracetamol hepatotoxicity in mice", *Pharmaceutical Research*, **30(5)**, pp.1252-1262.

[37] B.C. Yu, , W.C. Chen, J.T. Cheng (2003), "Antihyperglycemic effect of Andrographolide in streptozotocin-induced diabetic rats", *Planta Medica*, **69(12)**, pp.1075-1079.

[38] B.C. Yu, et al. (2008), "Mediation of β-endorphin in Andrographolide-induced plasma glucose-lowering action in type I diabetes-like animals", *Naunyn-Schmiedeberg's Archives of Pharmacology*, **377(4)**, pp.529-540.

[39] Z. Zhang, et al. (2009), "Hypoglycemic and beta cell protective effects of Andrographolide analogue for diabetes treatment", *Journal of Translational Medicine*, **7(1)**, pp.1-13.

[40] J. Xu, et al. (2012), "Synergetic effect of Andrographis paniculata polysaccharide on diabetic nephropathy with Andrographolide", *International Journal of Biological Macromolecules*, **51(5)**, pp.738-742.

[41] Y.L. Hsieh, et al. (2016), "Andrographis paniculata extract attenuates pathological cardiac hypertrophy and apoptosis in high-fat diet fed mice", *Journal of Ethnopharmacology*, **192**, pp.170-177.

[42] G.F. Dai, et al. (2011), "Anti-inflammatory effect of novel Andrographolide derivatives through inhibition of NO and PGE2 production", *International Immunopharmacology*, **11(12)**, pp.2144-2149.

[43] S. Peng, et al. (2016), "Andrographolide sulfonate ameliorates lipopolysaccharide-induced acute lung injury in mice by down-regulating MAPK and NF-κB pathways", *Acta Pharmaceutica Sinica B*, **6(3)**, pp.205-211.

[44] L. Dai, G. Wang, W. Pan (2017), "Andrographolide inhibits proliferation and metastasis of SGC7901 gastric cancer cells", *Biomed Research International*, DOI: 10.1155/2017/6242103.

[45] R.R. Malla, et al. (2019), "Terpenoids as potential targeted therapeutics of pancreatic cancer: Current advances and future directions", *Breaking Tolerance to Pancreatic Cancer Unresponsiveness to Chemotherapy*, Elsevier, pp.111-116.

[46] S. Harjotaruno, et al. (2007), "Apoptosis inducing effect of Andrographolide on TF-47 human breast cancer cell line", *African Journal of Traditional, Complementary and Alternative Medicines*, **4(3)**, pp.345-351.

[47] L. Ma, et al. (2012), "Effects of 14-alpha-lipoyl Andrographolide on quorum sensing in Pseudomonas aeruginosa", *Antimicrobial Agents and Chemotherapy*, **56(12)**, pp.6088-6094.

[48] T. Zhang, et al. (2017), "Inhalable Andrographolide-β-cyclodextrin inclusion complexes for treatment of Staphylococcus aureus pneumonia by regulating immune responses", *Molecular Pharmaceutics*, **14(5)**, pp.1718-1725.

[49] S. Pund, A. Joshi (2017), "Nanoarchitectures for neglected tropical protozoal diseases: Challenges and state of the art", *Nano-and Microscale Drug Delivery Systems*, Elsevier, pp.439-480.

[50] W.D. Tan, et al. (2017), "Is there a future for Andrographolide to be an anti-inflammatory drug? Deciphering its major mechanisms of action", *Biochemical Pharmacology*, **139**, pp.71-81.

[51] E.B. Kurutas (2015), "The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state", *Nutrition Journal*, **15(1)**, pp.1-22.

[52] P. Li, et al. (2014), "Self-nanoemulsifying drug delivery systems for oral insulin delivery: *in vitro* and *in vivo* evaluations of enteric coating and drug loading", *International Journal of Pharmaceutics*, **477(1-2)**, pp.390-398.

[53] R. Balamurugan, V. Duraipandiyan, S. Ignacimuthu (2011), "Antidiabetic activity of γ-sitosterol isolated from Lippia nodiflora L. in streptozotocin induced diabetic rats", *European Journal of Pharmacology*, **667(1-3)**, pp.410-418.

[54] C. Shen, et al. (2021), "Andrographolide attenuates established pulmonary hypertension via rescue of vascular remodeling", *Biomolecules*, **11(12)**, DOI: 10.3390/biom11121801.

[55] J. Chen, et al. (2017), "Loss of smooth muscle α-actin leads to NF-κB–dependent increased sensitivity to angiotensin II in smooth muscle cells and aortic enlargement", *Circulation Research*, **120(12)**, pp.1903-1915.

[56] T. Yang, et al. (2013), "Hypolipidemic effects of Andrographolide and neoAndrographolide in mice and rats", *Phytotherapy Research*, **27(4)**, pp.618-623.

[57] B. Shukla, et al. (1992), "Choleretic effect of Andrographolide in rats and guinea pigs1", *Planta Medica*, **58(02)**, pp.146-149.

[58] S.G. Wynn, B.J. Fougère (2007), "Veterinary herbal medicine: A systems-based approach", *Veterinary Herbal Medicine*, pp.291-409.

[59] M. Banerjee, et al. (2016), "Cytotoxicity and cell cycle arrest induced by Andrographolide lead to programmed cell death of MDA-MB-231 breast cancer cell line", *Journal of Biomedical Science*, **23(1)**, DOI: 10.1186/s12929-016-0257-0.