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Review Article

Bioactivities, Biopharmaceutics, and Advanced Drug Delivery Systems of Magnolol

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ABSTRACT

Magnolia bark is an important food supplement. Magnolol (ML), 3,3′-Neoligna-8,8′-diene-4,4′-diol, is a bioactive phenolic molecule found in the *Magnolia* family. Advanced Drug Delivery Systems (DDSs) have been able to enhance therapeutic efficacy and reduce adverse effects of plant-derived bioactive. In the first part of the review, the bioactivities, mechanisms, and clinical prospects of ML are described. A brief explanation of the mechanisms of anti-inflammatory, antioxidant, cardiovascular-protective, neuroprotective, and anti-cancer effects of ML is also provided. Later, the detailed biopharmaceutics of ML is described under solubility, dissolution, bioavailability, and pharmacokinetics. The solubility of ML in different media pH is also explained. The bioavailability of pure ML and its pharmacokinetics after parenteral and oral administrations are described. Further, pharmacokinetics after single and multiple doses of ML is also discussed. Finally, the reported advanced DDSs of ML are reviewed critically. Engineered crystals, solid dispersions, microstructures, and nanostructures of ML-loaded DDSs are reviewed.

Keywords: Biopharmaceutics, Drug delivery, Magnolol, Nanostructure, Pharmacokinetics.

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INTRODUCTION

Plant-derived foods and food supplements like *Magnolia* bark have established and important role in human health. Plant-derived bioactive agents have tremendously emerged and been approved in the last decade for clinical use as new drugs.[1,2] Herbal medicines containing these plant-derived bioactives have been used for so many years. Such herbal medicines are more popular in rural areas due to their wide availability and low cost.[3] Meanwhile, there are such traditional herbal medicines using the bark of *Magnolia officinalis* for thousands of years.[4] The natural compounds present in the *Magnolia* family have potential therapeutic activities. Therefore, they are used extensively in traditional medicinal and herbal preparations in Korea, China, and Japan.[5] Magnolol (ML) and honokiol are two major bioactive phenolic molecules found in *the Magnolia* family.[4] ML, chemically 3,3′-Neoligna-8,8′-diene-4,4′-diol (Figure 1), is a neolignan and mainly present in the barks of *Magnolia officinalis* or *Magnolia grandiflora*.[5]

Herbal medicines are reported to have significant bioactivity. However, administration of plant-derived bioactives is not without any adverse effects. A variety of adverse effects can be seen depending on the type of plant, delivery system, route of administration, and the dose administered. Kidney or liver damage, intestine perforation, cancer, or even death can be an adverse effect of herbal medicines.[6] Therefore, ML-based Drug Delivery Systems (DDSs) instead of ML-containing herbal medicines would be a good approach to attain the maximum therapeutic advantages of ML with the possible lowest adverse effects. A good number of advanced or novel DDSs are presently available which can be chosen depending on the dose, route of administration, disease, etc.

The advantages of advanced DDSs for herbal medicines are well known.[7] Advanced DDSs can enhance the biopharmaceutics of ML thereby enhancing its overall efficacy. Furthermore, the incorporation of ML into a DDS can reduce its adverse effects. This is particularly useful in the case of tumor-targeted delivery systems for anti-cancer bioactives such as ML. While crystal engineering itself has many advantages in enhancing the performance of drugs, the addition of polymers and conversion to delivery systems such as solid dispersions have some specific advantages. Enhancement of solubility and bioavailability are some common advantages of these approaches.[8,9] Nanotechnology-based DDSs have then emerged to solve many

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issues with conventional delivery systems for herbal medicines. Curcumin is a typical example of a bioactive highly explored in nanotechnology-based DDS.[10,11] The nanoscale (1 to 100 nm in general) dimensions of the nanostructures provided specific advantages for a variety of drug delivery applications. Meanwhile, nanoemulsion, among other nanocarriers, displayed tremendous applications owing to the presence of oil, surfactant, and aqueous phases. Nanoemulsions had a significant role in the conversion of bioactive to more soluble, stable, permeable, and bioavailable.[12,13] Furthermore, nanostructures also made significant advancements in achieving enhanced therapeutic efficacy of herbal bioactives. Polymeric nanoparticles for tumor-targeting were one among such advanced systems.[14] Interestingly, these and other advanced DDSs have been evaluated for ML in improving its solubility, bioavailability, therapeutic efficacy, tumor-targeting, etc.

Therefore, the present review describes the advanced DDSs for the enhancement of bioactivity or bioavailability of ML. Engineered crystals, solid dispersions, microstructures, and nanostructures of ML-loaded DDSs are discussed. Also, the biopharmaceutics of ML, which is a significant aspect of the development of its DDS, is described in detail. In addition, the details of bioactivities, mechanisms, and clinical prospects of ML are also included for a better understanding of the importance of ML-loaded DDSs. Figure 2 displays a summary of various aspects of ML described in this review.

Bioactivities, mechanisms, and clinical prospects of magnolol

Several studies have explored the bioactivities of ML and the mechanisms underlying such bioactivities. Anti-inflammatory, antimicrobial, antioxidant, cardiovascular-protective, neuroprotective, and anti-cancer activities are the widely studied bioactivities of ML (Figure 3). The anti-inflammatory activity of ML has been thoroughly studied for the last many years. Tumor Necrosis Factor Alpha (TNF-α) is considered a major regulator of inflammation and extreme activation of TNF-α signals causes chronic inflammation.[15] Therefore an ability to decrease the TNF-α level can favor and indicate anti-inflammatory activity of a compound. Interestingly, ML has shown such a decrease in TNF-α levels in several studies.[16-18] Meanwhile, Interleukin-1β (IL-1β), a pro-inflammatory cytokine, is an important mediator of inflammation.[19] Therefore, inhibition of IL-1β levels by ML shown in several studies also suggested its IL-1β-mediated anti-inflammatory activity.[17,20] It is well established that Cyclooxygenase-2 (COX-2) inhibition can provide significant anti-inflammatory activity.[21] The ability of ML to inhibit COX-2 was also demonstrated.[22] However, it has been later proven that derivatives resulting from COX-2 from naturally occurring omega-3 fatty acids have anti-inflammation activity.[23] Therefore, the acceptance of the anti-inflammation mechanism of ML through COX-2 inhibition may be a subject of future studies in this area. Meanwhile, inhibition of inducible Nitric Oxide Synthase (iNOS) expression was also observed during the anti-inflammatory activity of ML.[22] Interestingly, iNOS produces Nitric Oxide (NO) which has a very complex role in inflammation.[24] Thus, the anti-inflammatory activity of ML by inhibition of iNOS expression can be justified. Furthermore, inhibition of the levels of Interleukin 6 (IL-6), IL-12, Nuclear Factor kappa B (NF-κB), reactive oxygen species (ROS), intercellular Adhesion Molecule 1 (ICAM-1), p38, extracellular signal-regulated kinase 1/2 (ERK1/2), Stress-activated protein kinases/ Jun amino-terminal kinases (SAPK/JNK), phosphorylated-ERK (p-ERK), p-JNK, mitogen-activated protein kinases (MAPKs), p-p38, and p-IκBα was also demonstrated by several studies with ML.[16,18,25,26] Meanwhile, Zonula Occludens-1 (ZO-1) and occludin are barrier proteins working against inflammatory responses. It was observed that ML enhances the expression of both these barrier proteins and provides an anti-inflammatory response. Similarly, ML treatment enhances the levels of anti-inflammatory factor Proliferator-Activated Receptor-gamma (PPARγ).[17] All these suggested potent anti-inflammatory activity of ML by multiple mechanisms through several mediators. Importantly, these anti-inflammatory mechanisms have resulted in wide interest in the development of anti-inflammatory agents based on ML.[26]

Currently available antimicrobial agents have the threat of antibiotic resistance and therefore novel antimicrobial agents, plant-derived particularly, are under screening to overcome such situations.[27] Thus, the antimicrobial activity of ML is another thrust area where significant opportunities are available. Natural compounds with phenol groups, such as ML, show antimicrobial activities mainly through membrane toxicity.[28] Luckily, ML has shown both antibacterial and antifungal activities. Interestingly, ML has shown significant antibacterial activities against both Gram-negative (*Porphyromonas gingivalis* and *Prevotella intermedia*) and Gram-positive (*Micrococcus luteus* and *Bacillus subtilis*) bacteria.[29] Furthermore, ML has a significant effect on *Mycoplasma* species too. ML caused significant sunken and wrinkled cell membranes in *Mycoplasma*. Moreover, the metabolomic analysis showed a highly significant up-regulation of Protegenin A that can cause destruction of cell membrane integrity and cell activity in *Mycoplasma*.[30] Meanwhile, the antifungal activity of ML has been demonstrated in *Aspergillus, Trichophyton, Epidermophyton, Microsporium, Candida,* and *Cryptococcus* species.[31] Protein Kinase C (PKC) and Choline/ Ethanolamine Kinase 1-Mitogen-Activated Protein Kinases (CEK1 MAPK) pathways were established for the activity of Ml against *Candida albicans*. All these activities suggested significant and promising antimicrobial activities of ML.

The antioxidant effect of ML is another important bioactivity studied by both experimental and computational methods. Polyphenols are established dietary antioxidants.[32] A study has shown that ML can trap peroxyl radicals and such an effect emerges from the interactions of reactive OH groups in ML and

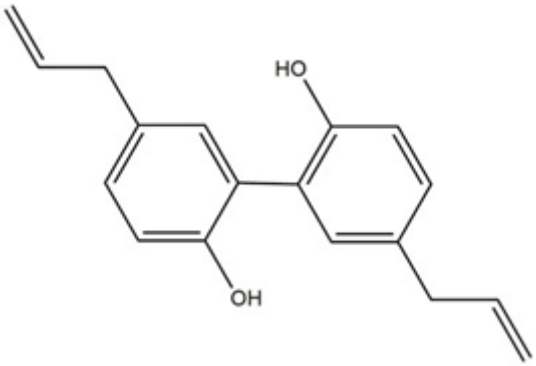

Figure 1: Chemical structure of magnolol (3,3′-Neoligna-8,8′-diene-4,4′-diol).

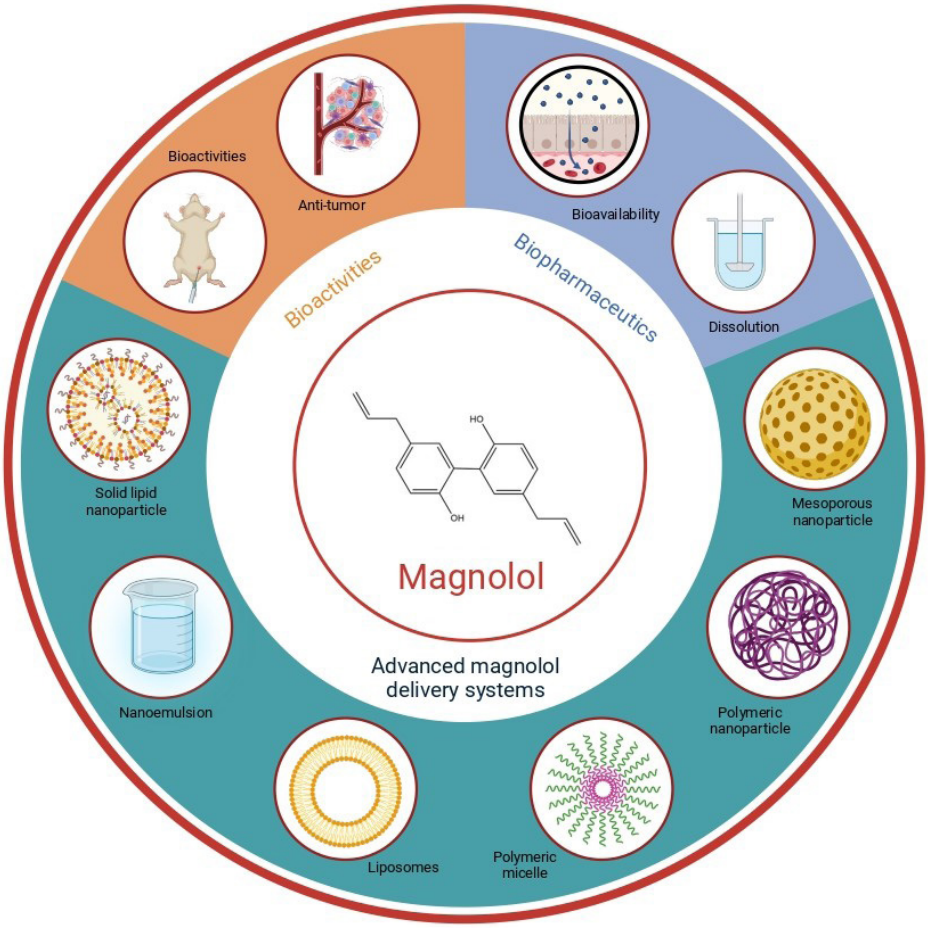

Figure 2: A pictorial summary of bioactivities, biopharmaceutics, and advanced drug delivery systems of magnolol described in this review.

the aromatic and allyl π-systems. Further, the combined effect of these interactions finally decides the total effect of the ML.[33] It is also reported that ML induces the production of antioxidant enzymes. Induction of activities of NAD(P)H: quinone oxidoreductase 1 and catalase enzymes by ML was noted and was dependent on the concentration of ML. Thus ML caused the suppression of hydrogen peroxide and 6-hydroxydopamine-induced toxicities.[34] Meanwhile, the *in vivo* antioxidant activity of ML was demonstrated in rabbits. The study was based on the antioxidant effect of ML which could cause inhibition of intimal thickening after causing balloon injury in hyperlipidemic rabbits. ML showed significant inhibition of intimal hyperplasia and MCP-1 expression. Thus, it was concluded that the antioxidant effect of ML can protect from postangioplasty restenosis.[35]

Cardiovascular protection is another important and established bioactivity of ML. In short, ML can show cardioprotective,

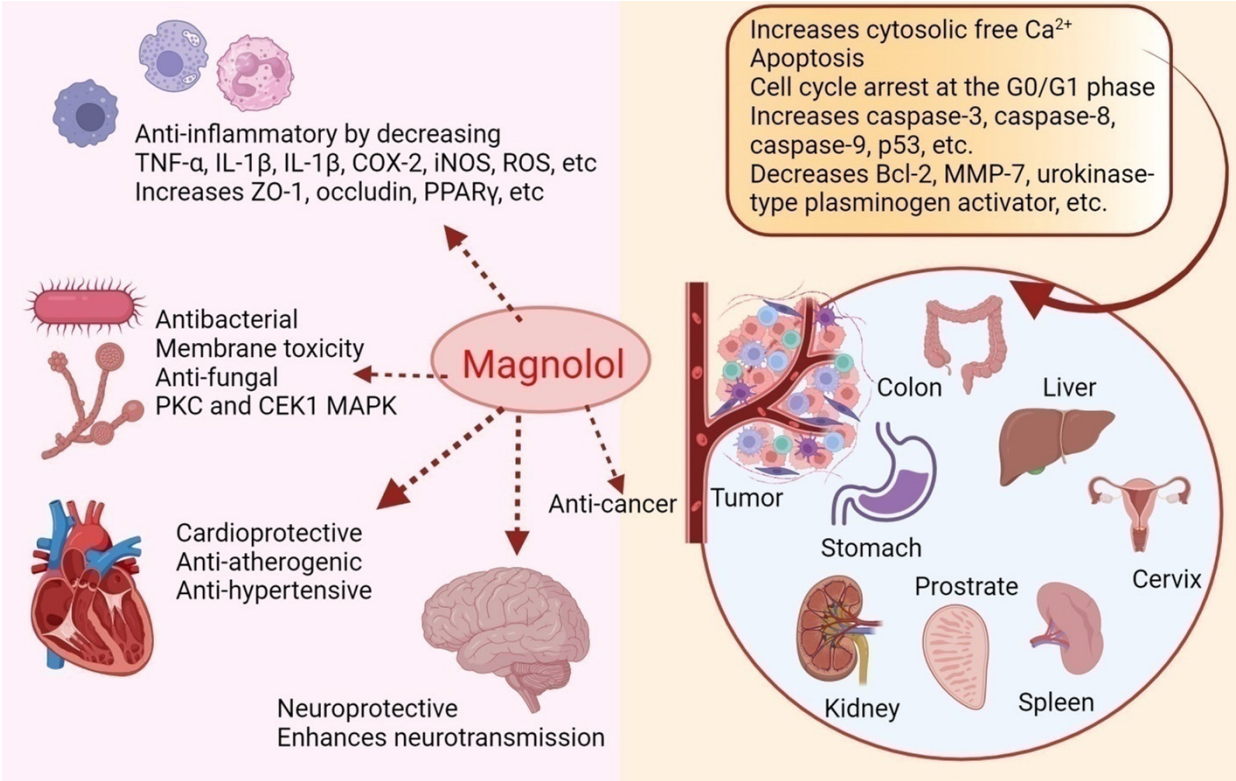

Figure 3: Pictorial representation of major bioactivities of magnolol and the mechanisms underlying such bioactivities.

anti-atherogenic, anti-hypertension, and inhibition of platelet aggregation and thrombus formation actions.[36] ML, when taken in small and moderate doses, can prevent heart damage from ischemia and reperfusion, lessen atherosclerotic alterations, shield endothelial cells from death, and prevent neutrophil-endothelial adhesion. The primary targets of ML at a moderate to high concentration are smooth muscle cells and platelets. ML suppresses proliferation at both moderate and high concentrations and causes apoptosis in vascular smooth muscle cells at a moderate concentration. A high ML concentration also prevents platelet aggregation, activation, and thrombus formation. However, only at very high concentrations does ML act as a smooth muscle relaxant. Given that ML can be taken orally to achieve the therapeutic dose for cardiovascular protection, it is a highly promising drug for the prevention of cardiovascular illnesses in high-risk individuals.[37]

The neuroprotective effect of neolignans in *the Magnolia officinalis* cortex provided some insights into the potential therapeutic uses of ML against brain disorders. Furthermore, ML protects neurons through reduction in Aβ toxicity, regulation of cholinergic nerve function, and anti-inflammatory and antioxidant activities. To preserve neurons, ML has the ability to control dopaminergic neurons and lessen αS poisoning. ML prevents inflammation and oxidative stress brought on by stroke by shielding Brain Microvascular Endothelial Cells (BMECs). It has been demonstrated that ML can cure anxiety and depression by regulating GABAergic neurons and modulating the HPA axis. ML generally works by shielding nerve cells and BMECs in order to prevent and treat brain illnesses. Furthermore, ML regulates acetylcholine and cholinesterase activities thereby protecting cholinergic neurons. Also, ML protects dopamine neurons and enhances Gamma-Aminobutyric Acid (GABA) neurotransmission. Enhancement of serotonergic neurotransmission is also observed by the action of ML.[38] Meanwhile, analyzing the neuroprotective benefits in adult male Sprague-Dawley rat models of intracerebral hemorrhage has demonstrated that ML lowers brain water content and repairs the blood-brain barrier. Because of these processes, there is a decrease in pro-inflammatory chemicals, neutrophil infiltration, and glial cell activation, which attenuates neurological impairments.[38] Meanwhile, neuroprotection by ML by β-amyloid toxicity in PC-12 cells is also found.[39]

Plant-derived anti-cancer agents are under continuous monitoring to explore all possibilities of development into new drugs for clinical use.[40,41] As a result, several phytochemicals have been identified as potential anti-cancer agents against specific cancer types.[42] Meanwhile, the cytotoxic action of plant-derived lignans and neolignans was also described.[43] Thus, ML was also under thorough investigation for its anti-cancer activities and has been proven to be effective against cancers of the brain, colon, liver, lung, breast, cervical, prostate, skin, etc.[44] ML has been shown to be effective against bladder cancer by several mechanisms such as inhibition of Matrix Metalloproteinase-9 (MMP-9), Cyclin -B1/CDC2, and Hypoxia-Inducible Factor-1α/Vascular Endothelial

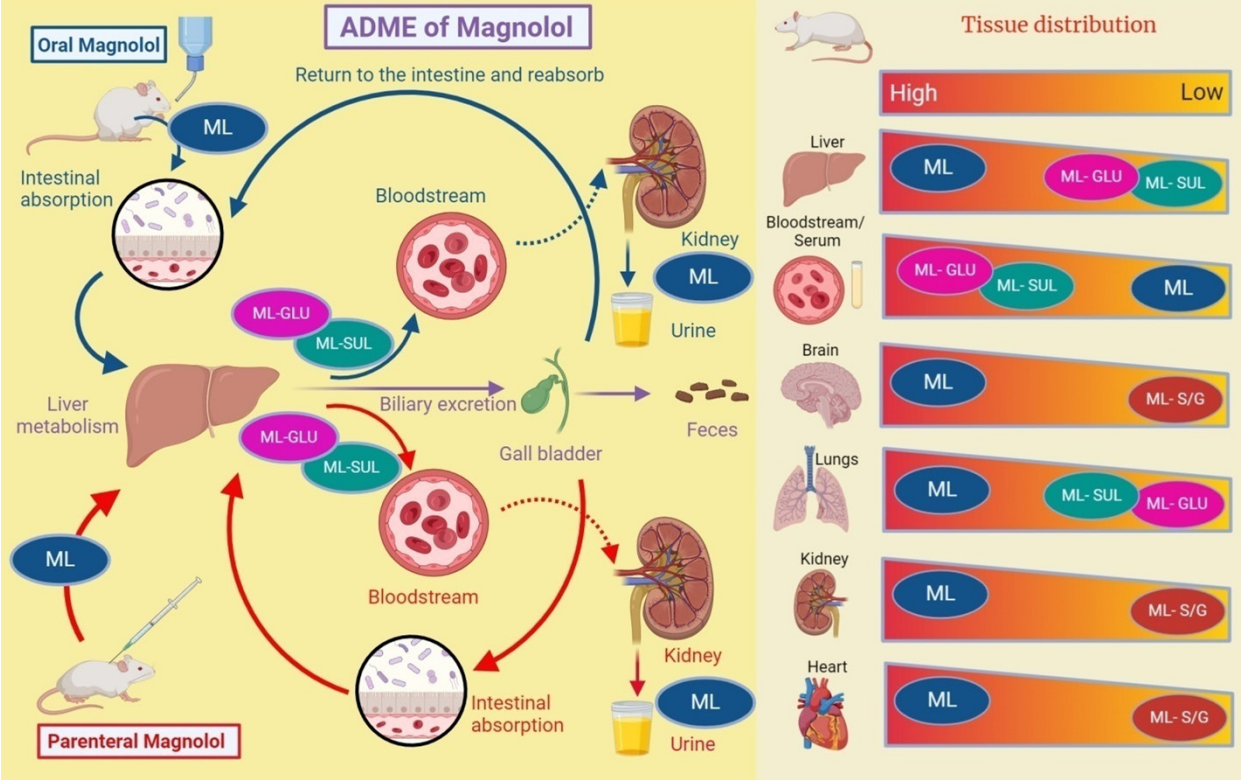

Figure 4: Pictorial representation of the Absorption, Distribution, Metabolism, and Excretion (ADME) of magnolol after oral and parenteral administrations. *In vivo* tissue distributions of magnolol, ML-Sulphates (ML-SUL), ML-Glucuronide (ML-GLU), and a mixture of ML-GLU and MG-SUL (ML-S/G) are also shown.

Growth Factor (HIF-1α/VEGF)- dependent angiogenesis pathways, when studied *in vitro.*[45-47] Further, ML enhances the expression of p27Kip1, a tumor suppressor, when tested *in vitro.*[47] Also, ML has shown promising results against bladder cancer during *in vivo* studies. Inhibition of HIF-1α/VEGF-dependent angiogenesis pathways and FoxO3 activation along with induction of IGF-1 have been noted for these results.[45,48] Meanwhile, *in vitro* inhibition of breast cancer cells by inhibition of lysyl oxidase, cell growth, MMP-9, NF-κB, Mitochondrial Membrane Potential (MMP), Bcl-2, cyclin-B1, and Cyclin-Dependent Kinase 1(CDK-1) have been shown by ML. It also causes cell cycle arrest at the G2/M phase, increased Reactive Oxygen Species (ROS), release of cytochrome c, miR-200c, Apoptosis-Inducing Factor (AIF), Bax, p21, and p53 showing significant *in vitro* anti-cancer activity against breast cancer cells.[49-52] Interestingly, inhibitions of MMP-9 and NF-κB by ML were observed *in vivo* also in a human breast cancer mice model.[52]

In the case of colon cancer cells, ML shows increased cytosolic free Ca^{2+}, translocation of cytochrome c, caspase-3, caspase-8, caspase-9, p53, Bax, AMP-Activated Protein Kinase (AMPK) activation, cell cycle arrest at G0/G1 phase, apoptosis, and p27Cip1 protein during *in vitro* studies. Meanwhile, ML decreased Bcl-2, β-catenin, MMP-7, urokinase-type plasminogen activator, and cytochrome–myc *in vitro.*[53-55] *In vivo* studies with ML have shown reduced tumor growth, invasion, and mobility of tumor cells, thymidine incorporation, and increased ERK phosphorylation and p21.[54,56] All these observations implied significant anti-colon cancer activity of ML. Meanwhile, ML has shown potential activities against liver cancer too, both *in vitro* and *in vivo*. Decreased tumor cell viability, tumor cell survival, and DNA synthesis were observed with ML treatment. Increased cytosolic free Ca^{2+}, apoptosis, and cell cycle arrest at the G0/G1 phase were also noted.[54,57,58] *In vivo* studies in mice also showed reduced tumor growth, cell invasion, and tumor cell metastasis.[59] Skin cancer is another area where the therapeutic applications of ML can be significantly explored. Both *in vitro* and *in vivo* studies have shown promising results of ML against skin cancer cells. *In vitro* studies have shown reduced cell proliferation. Also, decreased expression of Bax and Bcl-2was observed *in vitro* when treated with ML. Meanwhile, increased apoptosis, Growth Arrest-Specific 5 (GAS5), caspase-3, caspase-8, and caspase-9 were also observed on treatment with ML.[60-62] ML also showed *in vivo* effects of decreased tumor growth and decreased expressions of ERK-1/2, MAPK, PI3K/AKT, iNOS, and COX-2. Enhanced cell cycle arrest at the G2/M phase and enhanced expressions of poly(ADP-ribose) Polymerases (PARP) and p21 were some other *in vivo* responses of ML.[61,63] Similar mechanisms have been observed during *in vitro* and *in vivo* studies with ML related to oral, ovarian, prostrate, spleen, thyroid, melanoma, leukemia, kidney, cervical, gall bladder, and gastric cancers.[44] However, the studies exploring such anticancer activities of ML are mostly *in vitro*. Therefore, further pre-clinical and clinical studies

Table 1: Other recent reported anticancer activities and mechanisms of magnolol.

Sl. No.	Type of cancer	Major cytotoxic mechanism of ML on cancer cells	References
1	All types	Mitophagy through PINK1–pSer65-Ub–Parkin and LC3–OPTN/NDP52	64
2	Bladder	Upregulation of the miR-124; Inactivation of PKC-δ/ERK axis	65
3	Cervical	Targets PI3K/AKT/mTOR pathway; Targets epithelial-mesenchymal transition signaling	66
4	Gastric	Increases *Bax*, *p21* and*p53* expressions; Reduces *Bcl2* and expressions	67
5	Oral	Inhibits cancer stemness; Inhibits IL-6/Stat3 signaling	68
6	Oral	Release Ca^{2+} and causes Ca^{2+} influx in oral cancer cells	69
7	Pancreatic	Negative regulation of TGF-β/Smad signaling	70
8	Prostate	Antiandrogenic receptor effect; Binds to the androgen receptor; Inhibition of production of prostate-specific antigen	71
9	Skin	Inhibition of Ca^{2+}-permeable Transient receptor potential vanilloid-3 ion channels; Inhibition of inflammatory cytokine release	72
10	Triple negative breast cancer	Decreases metastasis and associated protein expression; Inactivates EGFR/ JAK signal	73

must be planned for further development of this highly potent plant-derived bioactive to establish and be approved as a new drug for cancer chemotherapy. In this regard, it is noteworthy that many of the novel DDSs of ML explore the opportunities to enhance its cytotoxicity for better cancer therapeutic applications. The other most recent updates of anticancer activities of ML are provided in Table 1.

Biopharmaceutics of magnolol

Solubility and dissolution

ML is very soluble in organic solvents such as benzene, dichloromethane, ethyl ether, chloroform, acetonitrile, ethyl acetate, and acetone. It also has good solubility in water-miscible organic solvents such as ethanol (20 mg/mL), DMSO (16 mg/mL), and dimethylformamide (20 mg/mL). As can be expected from the high solubility in organic solvents, it is poorly soluble in water. The aqueous solubility of pure ML is only around 0.12 mg/mL.[74,75] Meanwhile, ML is sparingly soluble in aqueous buffers. ML shows and an interesting solubility behavior depending upon the type and pH of aqueous buffers. The solubility of ML below a pH value of 7.4 is 16 µg/mL or less. However, on increasing the pH values of the buffer from 7.4 to 10, the solubilities of ML increased drastically. This enhanced solubility of ML at higher pH values can be attributed to the ionization of its phenolic groups rendering it more polar and soluble in an aqueous alkaline medium. In addition, the solubility of ML in borate buffer is slightly higher in phosphate buffer when tested at a pH of 8.[75]

Based on the above-discussed solubility, ML can be expected to show low and slow dissolution at lower pH values. Thus, the dissolution rate of ML in pH 6.8 buffer, even with Tween 80 as a solubilizer at a concentration of 0.005%, is very limited. ML shows only 8.2% dissolution at 45 min and 22.7% at 240 min.[76] A similar dissolution of pure ML of less than 12% after 120 min was also observed.[77] When the comparison of dissolution profiles of ML over a wide range of pH (phosphate buffers), 2.1, 6.0, and 8.0, was done for 300 min, the dissolution of ML was found to increase with time and pH. The concentration of ML in the dissolution medium and thereby the area under the dissolution curve were in the order of pH 2.1< pH 6.0 < pH 8.0.[78] Here also the effect is similar to the solubility and the dissolution is much higher at pH 8.0 compared to lower pH values.

Bioavailability and pharmacokinetics

The major implication of poor aqueous solubility and dissolution of any drug, including ML, will be on its bioavailability and pharmacokinetics. A poor aqueous solubility contributes towards a low bioavailability, except where permeability plays a key role. In the case of ML, a permeation-inhibitory effect too is known.[79] As a result, ML shows poor bioavailability. The absolute oral bioavailability of ML is less than 5%. However, there occurs a sharp increase in plasma-ML concentration when administered

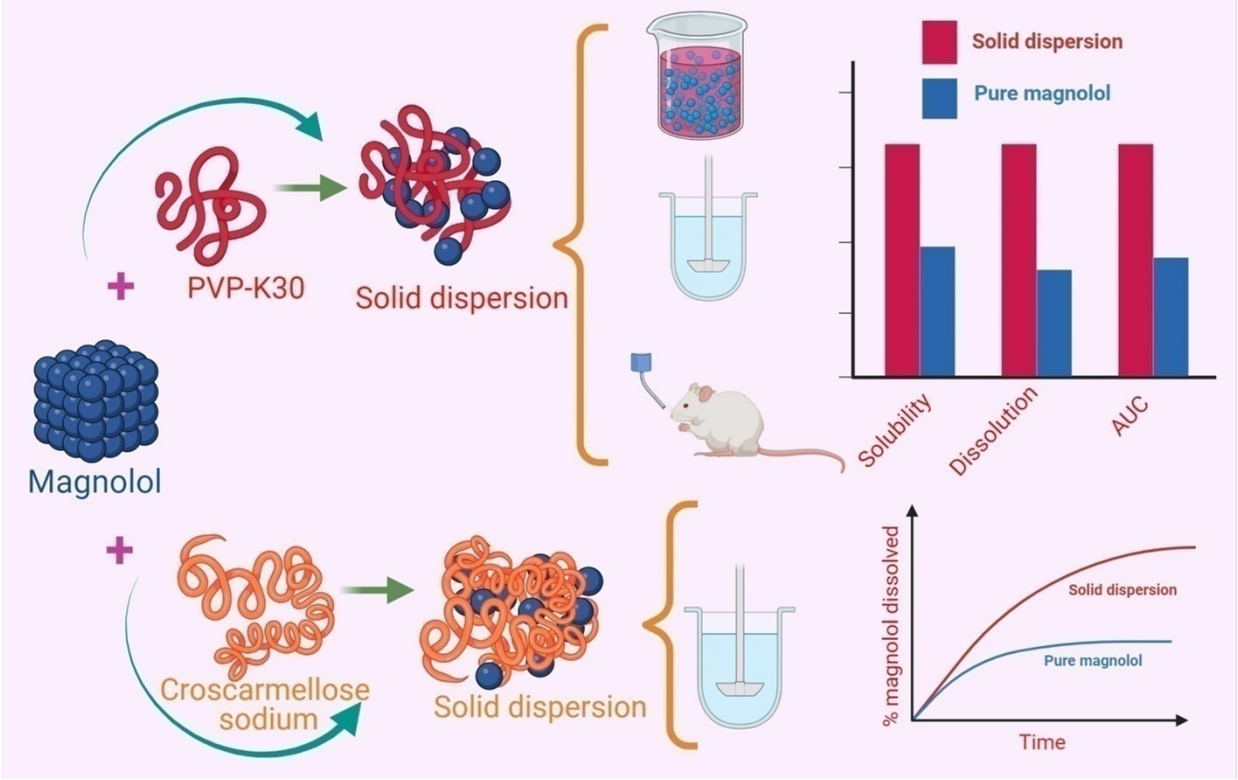

Figure 5: Diagrammatic representation of solid dispersions of magnolol with polyvinylpyrrolidone K-30 (PVP-K30) and croscarmellose sodium. The effect of solid dispersion on solubility, dissolution, and AUC are compared to pure magnolol.

orally.[80] The initial sharp increase could be due to the effect of the unionized form of ML in the low-pH gastric fluid. The stomach will be the major site of absorption for acidic drugs due to lower ionization subsequently resulting in low polarity of the drug molecule. However, the limited solubility of ML in the gastric fluid might have resulted in its poor bioavailability. The absorption of ML from the gastrointestinal tract through a lipid-like pathway is also suggested.[81] Meanwhile, the absorption mechanism through the intestinal part could be mainly by passive diffusion. However, the presence of a carrier-mediated passage is also suspected as a minor pathway.[82] A significant increase in the area under the curve for the dissolution profile is shown by ML at higher pH values simulating the alkaline-intestinal pH.[78] However, this could not directly enhance the *in vivo* absorption of ML, probably due to rendering the molecule more polar and subsequently lowering its permeability characteristics.

The pharmacokinetics of ML is most explored from pre-clinical models. An enterohepatic circulation of ML has been confirmed by the presence of multiple peaks in plasma-ML concentration profiles and the major metabolite is magnolol-2-O-glucuronide.[80,83] ML-Sulphates (ML-SUL) and ML-Glucuronide (ML-GLU) forms are most abundant after oral administration of ML. Administered ML is immediately metabolized by the liver and ML-GLU is the major form detected in the blood.[84] As a result, the predominant route of elimination of ML (> 90% of dose) after oral or parenteral administration is through the feces. In addition to these, induction of metabolic enzymes also occurs with ML as shown by the significant increase in metabolites after repeated doses.[83]

It is proposed that ML follows a first-order one-compartment model after oral administration. The *in vivo* Area Under the Curve (AUC) for ML in rats after oral administration at a dose of 20 mg/kg is 0.75±0.10 μg.h.mL^{-1}. Meanwhile, the first-order absorption rate constant (k_a) and first-order absorption rate constant (k) are 0.63±0.35 h^{-1} and 2.33±0.34 h^{-1}, respectively. Further, the T_{max} was 1.12±0.48 h and the C_{max} was 0.16±0.02 μg.mL^{-1}.[80] When the same dose of 20 mg/kg of ML was administered intravenously as emulsion in rats, the $AUC_{0\text{-}24h}$ for ML was 6801±1057 μg.h.mL^{-1} and $AUC_{0-\infty}$ was 6875±1080 μg.h.mL^{-1}. Meanwhile, the Mean Residence Time (MRT) was 1.7±0.3 h. Further, it showed a $T_{1/2}$ of 5.49±1.77 h. The apparent volume of distribution and clearance values were 0.37±0.059 mL/kg and 2.9±0.9 mL/h/kg, respectively.[85] Further, in the case of intraperitoneal administration at an ML dose of 100 mg/kg in rats, ML had shown $AUC_{0-12\,h}$, $AUC_{0-\infty}$, T_{max}, C_{max}, and $T_{1/2}$ values of 2582.67±150.48 μg×min/mL, 4016.90±535.62 μg×min/mL, 64.06±6.88 min, 5.10±0.65 μg×min/mL, 460.88 ± 37.41 min, respectively.[86]

In the case of ML, the pharmacokinetics of the metabolites is equally important to the free drug. Such an approach of studying the pharmacokinetics of the metabolites of ML in comparison to free ML would provide further insights. Further, it is very useful and critical for the drug development process.[87] After

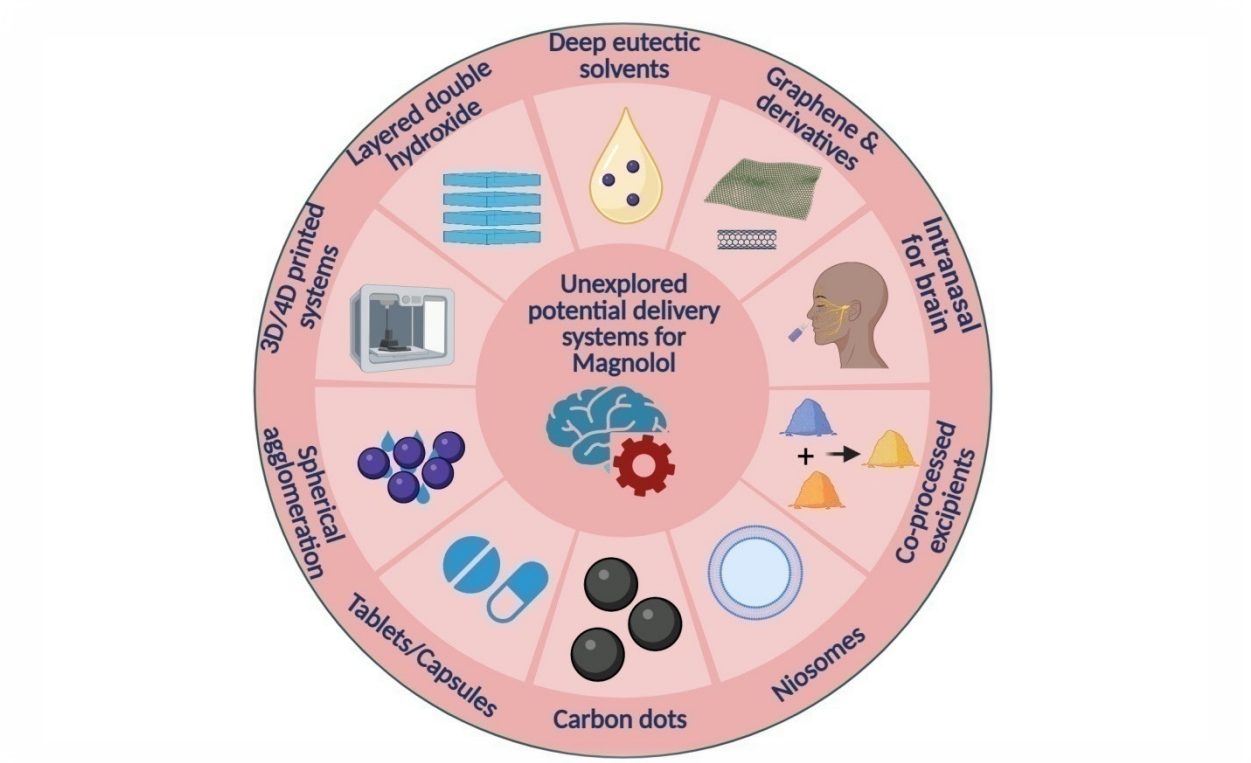

Figure 6: A diagrammatic presentation of some unexplored and potential drug delivery systems suitable for magnolol and that can form research ideas for future studies.

intravenous administration at a dose of 20 mg/kg in rats, ML is instantaneously metabolized mainly to ML-GLU, MG-SUL, or a mixture of ML-GLU and MG-SUL (ML-S/G). The major part of circulated ML was in the form of ML-GLU metabolite. Meanwhile, the $AUC_{0\text{-}480min}$ for ML and ML-GLU were 2319.2±536.9 and 3082.4±687.4 nmol·min/mL, respectively. This indicates that both ML and ML-GLU are almost equally present in systemic circulation. Likewise, ML and ML-S/G were detected after oral administration of a single dose of 50 mg/kg in rats. After oral administration too, similar to intravenous, the major conjugate is ML-GLU and the presence of ML-SUL is negligible. Also, the major part of circulated ML was in the form of ML-GLU metabolite with the $AUC_{0\text{-}480min}$ value of 1244.5±186.9 nmol·min/mL. This value is very high compared to that observed for ML (228.5±23.2 nmol·min/mL). Similar to intravenous administration, oral administration also favors significantly higher values of ML-S/G for $AUC_{0\text{-}480min}$ (350%) compared to free ML. In the case of C_{max}, ML-S/G has a 180% value of free ML. Thus, after oral administration significantly higher quantities of ML-GLU reach the systemic circulation compared to ML whereas during intravenous administration both forms are almost equally present in the systemic circulation.[88]

In addition to unveiling the pharmacokinetics of single-dose administration, multiple-dose studies are more appropriate for further detailing the pharmacokinetics and are suitable for tailoring the treatment regimen for clinical settings. Further, it is more appropriate for bioequivalence evaluation than single-dose studies.[89] Luckily, the data for the pharmacokinetics of ML and its metabolites after seven oral doses of 50 mg/kg (thrice daily for seven doses) is also available for comparison with single-dose studies. As observed for single-dose studies, a significantly higher value of ML-S/G for $AUC_{0\text{-}480min}$ (584%) compared to free ML was observed after the seventh dose. Meanwhile, a significantly higher value of ML-S/G for C_{max} (606%) compared to free ML was also observed after the seventh dose. However, the single dose of ML produced higher C_{max} compared to that observed for the seventh dose.[88]

The tissue distribution of drugs has many aspects on pharmacokinetics. It depends on the rate of blood flow, passage of drugs through different membranes, and distribution to tissues. This can cause a decrease or increase of drug in a specific tissue depending on several factors and thus can affect pharmacokinetics.[90] It has been demonstrated that the highest concentration is observed in the liver for both ML and ML-S/G after oral administration in rats. Also, the mean level of ML in the liver is higher compared to that of ML-S/G.[88] This might be due to the higher uptake of ML by the liver for conjugation reactions. However, the presence of ML in serum is significantly lower than ML-S/G.[88] This effect could be considered as an effect of the release of conjugated ML-S/G into the systemic circulation. However, the presence of ML in the brain is significantly higher than ML-S/G. This could be easily justified by the increased polarity of ML-S/G

rendering it unable to cross the blood-brain barrier effectively. It is noteworthy that in both the serum and liver, the presence of ML-GLU is significantly higher than ML-SUL. Meanwhile, the lung also shows significantly higher levels of free ML compared to ML-S/G. However, interestingly, the presence of ML-SUL in the lungs is significantly higher than ML-GLU.[88] The high rate of sulfate conjugation of drugs by lung tissues is well reported and can be considered for the presence of higher ML-SUL than ML-GLU in the lungs.[91,92] As expected, the presence of very high biodistribution of free ML and negligible quantity of ML-S/G is observed in the kidney. The molecular weight of ML, ML-GLU, and ML-SUL are 266.340, 442.458, and 346.398 g·mol^{-1}, respectively. Generally, it is considered that drugs or metabolites with a molecular weight of <300 g·mol^{-1} undergo predominantly renal excretion whereas those with a molecular weight of >300 g·mol^{-1} undergo biliary excretion. Thus, the negligible quantity of ML-S/G in the kidney is well reasonable. Finally, the free ML shows significantly higher distribution in the heart compared to ML-S/G. The high affinity of polyphenols, like ML, to highly perfused organs such as the heart be could the possible reason for such an observation.[93] Figure 4 illustrates a summary of the ADME and tissue distribution profile of ML.

Advanced drug delivery systems of magnolol

Engineered magnolol crystals

Crystal engineering can be employed to alter several physicochemical parameters such as solubility, permeability, compaction, and bioavailability of a drug. Such crystal engineering can have an important role in pharmaceutical development.[94] Crystal engineering tunes the physical and mechanical properties of drugs.[95] Co-crystallization is an example of such an approach and is an acceptable approach for scale-up and manufacturing processes.[94] Meanwhile, eutectics are novel material composites with low melting points in comparison to the individual components and present another important approach in pharmaceutical development.[96] Instead of simply enhancing any physicochemical properties such as solubility, tuning these properties to desired levels is more acceptable and attractive for pharmaceutical development. In an interesting report, mechanochemistry was employed for such an approach with ML employing co-crystallization and eutectic. Three isomers of pyridine amides, nicotinamide, isonicotinamide, and picolinamide were used for the preparation of multicomponent crystalline solids with ML. The co-crystals prepared with nicotinamide and isonicotinamide were isostructural in nature. Meanwhile, the eutectic was prepared with picolinamide. The solubilities after 300 min at pH 8.0 were 24.574 and 19.467 µg/mL for ML-nicotinamide and ML-isonicotinamide co-crystals, respectively. Meanwhile, it was 16.832 µg/mL for ML- picolinamide eutectic. Thus, the dissolution of ML from ML-based multicomponent crystalline solids followed the order ML-nicotinamide > ML-isonicotinamide > ML- picolinamide in pH 8.0. A similar pattern was also observed for dissolution in media pH values of 2.1 and 6.0. Furthermore, the extent of ML dissolution followed the order 8.0 > 6.0 > 2.1. It was further demonstrated that the *in vitro* antibacterial effects of these ML-based multicomponent crystalline solids on *Escherichia coli* and *Bacillus subtilis* are more effective than pure ML. The accelerated stability studies confirmed the physical and chemical stability of all the studied ML-based multicomponent crystalline solids.[78] Thus, the study provided an option for the delivery of ML as an effective antibacterial agent. This study could be beneficial for the further development of ML-based systems for effective treatment strategies. However, the precise control of the co-crystals and eutectic needs a thorough understanding of the crystal engineering principles, and further studies in this direction would be beneficial for achieving a clinically successful ML-based co-crystal or eutectic. The selection of the appropriate polymorph can be another challenge to overcome.

Solid dispersion

Formulation of solid dispersions can be considered as the immediate alternative to crystal engineering wherein definite enhancement of solubility and bioavailability are the major requirements. This is a solubilization technique using a polymer and results in the formation of a two-component system of drug and polymer.[97] Such an approach was demonstrated with polyvinylpyrrolidone K-30 and ML. The solubility of ML was found to increase with an increase in the concentration of polyvinylpyrrolidone in the solid dispersion prepared with these components by the melting method. The solid dispersion prepared in the drug: polymer ratio of 1:1showed significantly enhanced dissolution of ML in 0.1 N HCl, pH 4.5 buffer, and pH 6.8 buffer compared to that from pure ML and a physical mixture of the ML and polymer. Furthermore, this solid dispersion significantly increased the oral bioavailability of ML in rats. Compared with those after oral administration of pure ML, the relative presence of ML and ML-S/G in rabbit blood was enhanced by 80.1 and 142.8%, respectively after oral administration of the solid dispersion. After oral administration of solid dispersion at an ML dose of 50 mg/kg, $AUC_{0-24\,h}$, MRT, T_{max}, C_{max}, for ML were 679.0±130.0 nmol×min/mL, 714.9±43.7 min, 275.0±272.6 min, 0.6±0.1 nmol×min/mL, respectively. Meanwhile, $AUC_{0-24\,h}$, MRT, T_{max}, and C_{max} for ML-S/G were 2170.5±1055.2 nmol×min/mL, 726.2±34.1 min, 420.0±211.3 min, 2.6±1.6 nmol×min/mL, respectively.[98] This study proved a promising approach through solid dispersion of ML for enhancement of its solubility and bioavailability.

In a similar attempt for solid dispersion, croscarmellose sodium with ML was also tried. The solid dispersion prepared in the drug: polymer ratio of 1:5 showed ML in dissolution of 80.66% after 120 min when tested. This percent dissolution was 6.9 times that obtained from pure ML. The amorphous nature of ML in the solid

dispersion was confirmed by differential scanning calorimetry, infrared spectrometry, and scanning electron microscopy studies. Furthermore, the solid dispersion was found to be stable in terms of dissolution and ML content even after six months of accelerated stability testing.[77] This study proved the possibility of improving the dissolution and stability of ML. The significance of the reported solid dispersions of ML with PVP-K30 and croscarmellose sodium is shown diagrammatically in Figure 5. However, the solid dispersions of ML can be challenging due to the lack of reproducibility and difficulty of incorporation into a dosage form. Furthermore, scale-up and large-scale production could be very expensive for solid dispersions. All these challenges can limit the further development of ML-loaded solid dispersions.

Microstructures

Mesoporous silica has certain attractive and unique properties for drug delivery applications. High specific surface area is one of these important properties. Moreover, mesoporous silica of different morphologies and pore structures are also available. Mesoporous silica has pores with sizes from 2 nm to 50 nm. Interestingly, the SBA-15 variety of mesoporous silica can have a Particle Size (PS) of less than 150 μm and a pore diameter of 5-15 nm. Further, a high internal surface area of around 400–900 m^2/g renders it a suitable material for a variety of applications.[99] Subsequently, drug loading was successfully tried using the SBA-15 variety of mesoporous silica. An enhanced release of fenofibrate was observed when loaded to SBA-15 mesoporous silica.[100] In the case of ML, prolongation of the release of ML was observed when it was loaded in amino-functionalized SBA-15 mesoporous silica. ML was loaded by suspending the amino-functionalized or un-functionalized SBA-15 mesoporous silica in an alcoholic solution of ML. The unloaded ML was removed by the processes of decantation and filtration and the ML-loading was determined by high-performance liquid chromatography. When *in vitro* dissolution testing was done in simulated gastric fluid for the first 2 hr and in simulated intestinal fluid pH 6.8 for the next 22 hr, both the amino-functionalized or un-functionalized SBA-15 mesoporous silica particles loaded with ML prolonged its release compared to pure ML. Among the samples, the amino-functionalized SBA-15 mesoporous silica was more efficient in prolonging the ML release compared to the un-functionalized SBA-15 mesoporous silica particles. It was further stated that the electrostatic interactions with the functional group retards the ML release.[101] The study was interesting in the aspect of exploring the potential of mesoporous silica. However, a thorough study of other aspects such as type and extent of functionalization also needs thorough investigation. Furthermore, the results of fenofibrate and ML were not in agreement. Thus, a huge research gap is evident in the development of mesoporous silica-based systems for ML.

Nanostructures

Nanostructure-based drug delivery has tremendously progressed in the last decade for a variety of drug delivery applications. Enhancement of solubility in aqueous media and penetration in the tissues, facilitating easy cellular uptake, and ensuring targeted delivery are some of the most explored advantages of nanostructures for drug delivery.

Nanosuspensions

Nanosuspensions can be considered as the simplest form of nanostructured DDS wherein the nanosized drug particles itself form the delivery system.[102] They are considered nanostructures without any matrix excipients.[103] It is a proven approach for the betterment of poorly soluble drugs. Specifically, nanosuspensions are ideal for plant-derived bioactive agents.[104] A solubility enhancement and faster release of ML were observed when its nanosuspension was prepared by solvent-anti solvent precipitation method and Pluronic F68 as the stabilizer. The solubility of ML from nanosuspension was 9.54 mg/mL which is almost 78 times solubility of the pure ML. Furthermore, the nanosuspensions with a mean PS of 35 nm had an ML release rate of 85.70% within 60 min in phosphate-buffered saline when studied by a dialysis method. Moreover, it was noted that the release rate is inversely proportional to the PS of the nanosuspension.[74] When nanosuspensions of ML were prepared with Soluplus® and Poloxamer 188, a PS of 78.53 ± 5.4 nm, Polydispersity Index (PI) of 0.04 ± 0.01, and Zeta Potential (ZP) of −24.27 ± 0.22 mV were noted. The drug loading for this nanosuspension was very high with a value of 42.50 ± 1.57%. Furthermore, the nanosuspensions showed ML release of 99.6 and 99.1% at pH 1.2 and 6.8, respectively after 24 hr. These values were higher compared to 84.6 and 91.1% under similar situations shown by pure ML. Moreover, the nanosuspension of ML showed higher C_{max} for ML than that from its mixed micelles using Soluplus® and Poloxamer 188.[105] Interestingly, there are also possibilities for sustaining the ML release by means of nanosuspension formulations.[104] Such an approach with ML is yet to be explored.

Nanoemulsion and self-microemulsifying drug delivery system

Nanoemulsions or microemulsions are a superior choice and are widely used for solubility and bioavailability enhancement of poorly water-soluble drugs. Hence, they are particularly useful for the oral delivery of poorly water-soluble plant-derived drugs.[106] They contain aqueous, surfactant/co-surfactant (S_{mix}) and oil phases. Importantly, they have homogeneity and thermodynamical stability. Furthermore, they are isotropic in nature. All of these make them an attractive drug delivery carrier for plant-derived bioactives such as ML.[12] A nanoemulsion formulation was prepared with an extract containing 78.5% ML. The oil and aqueous phases in the emulsion were 20 and 80% w/w, respectively. Moreover, the aqueous phase contained 1%

w/w Tween 80 as the surfactant. 1,2-propanediol was supposed to act as the co-surfactant in the formulation. Initially, the oil phase with the co-surfactant was mixed at 60°C with a magnetic stirrer maintained at 1300 rpm for 20 min. Later it was subjected to probe sonication (400 W, 30 min) and finally high-pressure homogenized (300 bar - 3cycles and 1000 bar - 6 cycles). The obtained nanoemulsion had a mean droplet size of around 300 nm. The emulsion was further sterilized at 121°C for 10 min after filling into vials. The ML content in the nanoemulsion was 2.0% w/v. The pharmacokinetic parameters of ML from nanoemulsion after intravenous and oral administrations were determined. After oral administration of nanoemulsion at an ML dose of 40 mg/kg, $AUC_{0-24\ h}$, $AUC_{0-\infty}$, MRT, half-life, T_{max}, C_{max}, apparent volume of distribution (Vd/F), and total clearance (CL/F) for ML were 2416±923 ng×h/mL, 2665±1306 µg×h/mL, 7.0±1.4 h, 4.9±3.0 h, 1.2±1.6 h, 426.4±273.8 ng/mL, 13.9±5.1mL/kg, and 2.2±1.0 mL/h/kg, respectively. The absolute bioavailability of ML was 17.5±9.7%. The study further demonstrated that ML was better absorbed from the gastrointestinal tract in the form of nanoemulsion.[85] This study was mainly intended for the simultaneous estimation of ML and honokiol (a positional isomer of ML, 3,5′-diallyl-4,2′-dihydroxybiphenyl) in rat plasma. However, it gave valuable insights into the nanoemulsion formulation of ML. Nevertheless, more studies are required for further optimization of oil, surfactant, and co-surfactant for nanoemulsion of ML with optimum characteristics and performance. Recently, an oral self-microemulsifying DDS of honokiol has been reported, and based on the structural similarity between honokiol and ML, it can be reasonably expected that such an oral self-microemulsifying system would work for ML too.[107]

Polymeric nanoparticles

The major advantages of polymeric nanoparticles for cancer chemotherapy include the possibility of manipulation of particles, targeting cancer cells, controlling the drug release, and minimizing the effect on normal cells.[108] In an early attempt, ML-loaded core-shell hydrogel nanoparticles were studied for prevention against balloon injury-induced migration of vascular smooth muscle cells along the injured artery wall. The core phase of the nanoparticles was formed by ML and polyvinylpyrrolidone. This core phase was encapsulated in the amphiphilic carboxymethyl-hexanoyl chitosan shell to form the ML-loaded core-shell hydrogel nanoparticles. The study employed three different loading amounts of ML while keeping the amount of carboxymethyl-hexanoyl chitosan constant. For an ML load of 0.2 mg/mL, these core-shell nanoparticles had a mean PS of 419 nm, PI of 0.18, ZP of -27.63±1.07 mV, and ML entrapment efficiency of 79.3±2.2%. The core-shell spherical structure of the nanoparticles was confirmed by electron microscopy images. Further, the drug release in phosphate-buffered saline containing 0.1% Tween 80 by a dialysis bag method showed that a higher content of carboxymethyl-hexanoyl chitosan slowed the ML release, providing an option for prolongation of ML release. Notably, a temperature-dependent release of ML was achieved from the core-shell hydrogel nanoparticles with a slower release at a lower temperature. The core-shell hydrogel nanoparticles were evaluated in A-10 cell lines and found that they undergo high cellular uptake. Also, they showed an antiproliferative effect and significant inhibition of vascular smooth muscle cell mobility.[109] Thus, the encapsulation of ML in core-shell hydrogel nanoparticles proved better than pure ML in cellular uptake and inhibition of cellular migration. However, the use of methanol in the preparation of the core phase in the study can have concerns about residual methanol content. Therefore, further evaluation of alternative solvents and polymers could be more useful in achieving better results with higher safety. In addition, the attachment of targeting ligands could also enhance the effectiveness of the delivery system. Furthermore, preclinical and clinical studies are also needed for further understanding of this approach.

Zein nanoparticles with anticancer agents have been found effective against several cancer cell lines such as SW480, Bel-7400, MCF-7 cells, HL60 cells, SCC40 cells, HeLa cells, Colo 205 cells, KB cells, A549 cells, hK562 cells, and HEK293 cells.[110] ML-loaded core-shell nanoparticles of zein with chondroitin sulfate coating have shown excellent targeting of macrophages and enhancement of colon-epithelial cellular uptake. These nanoparticles had a mean PS of 142.27±5.11 nm, ZP of -31.96±1.72 mV, ML entrapment efficiency of 80.71±0.44% and ML loading of 10.11±0.05%. Further, the nanoparticles appeared two-layered in the transmission electron microscope image. The chondroitin sulfate-coated nanoparticles showed high CD44 receptor-mediated uptake of nanoparticles in NCM 460 and raw 264.7 cells. CD44 receptors are highly expressed under inflammation and this demonstrated the high uptake of chondroitin sulfate-coated nanoparticles by tissues having inflammation. Moreover, it was further demonstrated that embedding these nanoparticles into hydrogel microspheres prolongs retention on inflamed surfaces in the colon. The embedding of these nanoparticles into sodium alginate and xanthan gum hydrogel microspheres was carried out by electrospraying and subsequent solidification with a 2% calcium chloride solution. These hydrogel microspheres had a mean PS of 164.36±6.29 µm. Importantly, these hydrogel microspheres were stable in simulated gastric and intestinal fluids and decomposed rapidly in simulated colonic fluid. Furthermore, the ML release from simulated colonic fluid after 24 hr was nearly complete. These microspheres showed improved retention and permeation in the gastrointestinal tract and improvement in dextran sulfate sodium-induced colitis when tested *in vivo* in mice. Furthermore, these microspheres showed improved anti-inflammatory effects *in vivo* by regulating the levels of TNF-α, IL-1β, IL-6, and IL-10.[111] Overall, the study demonstrated an enhanced anti-ulcerative colitis effect of the developed ML-loaded system. However,

exploring the storage stability of the developed systems and the suitability of other polymers or targeting agents for the purpose would be beneficial in further tailoring this interesting approach for enhancing the therapeutic potential of ML. Recently, shellac/zein/ML nanoparticles have been reported with good thermal stability, excellent 2,2-Diphenyl-1-picrylhydrazyl radical scavenging, and antifungal activities. The optimized nanoparticles had a PS of 2.84±0.03 nm, PI of 0.71±0.06, ZP of −29.61±0.67 mV, entrapment efficiency of 79.18 ± 0.61%.[112] However, these nanoparticles were developed for the purpose of preservation of berries and not drug delivery. Also, the PI was not in an acceptable range for drug delivery applications. Nevertheless, the results of these studies can be employed for the development of DDSs for ML.

In another interesting approach, chitosan-based nanoparticles were prepared and studied. In the study, ML-loaded nanocapsules were prepared and these nanoparticles were embedded in ML-grafted chitosan hydrochloride hydrogels. The purpose of the formulation was the incorporation of ML into hydrogel dressing to promote wound healing. Grafting of ML to chitosan was proposed to enhance its stability, aqueous solubility, and bioactivity. Also, the significant antibacterial and antioxidant properties of ML would be beneficial for use in wound healing dressings. Meanwhile, the nanoencapsulation of ML was aimed to prolong its release and enhance its stability in hydrogel dressing for wound healing. As a first step, the ML-loaded chitosan nanocapsules were prepared using oxidized sucrose for cross-linking. These nanocapsules were spherical in morphology and had a mean PS of 232.6±9.1 nm, PI of 0.50±0.13, ML entrapment efficiency of 82.3 ± 1.9%, and ML loading of 15.7 ± 0.5%. In the next step, the preparation of hydrogel of ML-grafted chitosan, ML-grafted chitosan with a grafting rate of 284.7 ± 25.9 μmol/g was used. For the successful grafting of ML to chitosan, a carboxyl-bearing ML derivative was coupled by using an EDC/NHS coupling reaction. The grafting of ML caused a reduction in the hydrophilicity of chitosan. The stability of the hydrogel during the swelling was enhanced by cross-linking with genipin. The ML release from the hydrogel was similar at pH 6.2 and 7.4. The pH responsiveness of the ML-loaded chitosan nanocapsules was demonstrated by a rapid release of MLat pH 6.2 (87.4%) compared to that at pH 7.4 (36.1%). Furthermore, the hydrogel showed did not show any significant cytotoxicity when tested in L929 cells. The comparative wound healing effect of the hydrogel was carried out in a splint excision dermal wound model of rats. A large number of new blood vessels and collagen fibers composed of fibroblasts were observed in wounds treated with the hydrogel formulation. Also, a denser and more uniform distribution of collagen fibers was observed. All these observations indicated a significant promotion of tissue proliferation by the hydrogel. Overall the system demonstrated enhanced antioxidant and antibacterial properties and reduced cytotoxicity rendering it suitable for application in wound dressings.[113] Even though the study was promising in terms of wound healing, a significant enhancement of antibacterial activity could not be achieved with this system. Therefore, further modifications in this system to enhance antibacterial activity would enhance the usefulness of the system for wound dressings.

ML-loaded polymeric nanoparticles have been developed for cancer therapy too. Cholesteryl biguanide conjugate hydrochloride was prepared to act as both a drug and a carrier for ML. The compound had anticancer activity and could load ML. Thereafter, polymers were added to ML-loaded cholesteryl biguanide conjugate hydrochloride to form nanoparticles. Nanoparticles formed with aminoethyl anisamide-poly(ethylene glycol)-poly(lactic-co-glycolic acid) to poly(ethylene glycol)-poly(lactic-co-glycolic acid) ratio of 4:1 showed good accumulation in tumor tissues. Meanwhile, the conjugate and ML also showed synergistic inhibition on 4T1 cells. Furthermore, these nanoparticles showed significantly high tumor cell uptake, apoptosis, and inhibition of tumor cell migration. The nanoparticles showed continuous accumulation in the 4T1 tumor in mice within 48 hr. When administered intravenously to mice with 4T1 breast tumors *in situ*, the nanoparticles showed inhibition of tumor growth without notable toxicity.[114] Thus, the study was promising in providing a synergistic drug-carrier combination against triple-negative breast cancer. Meanwhile, it would be further interesting to unveil the effect of other lipid-based biguanide conjugates against triple-negative breast cancer.[114]

In yet another recent and interesting study on the synergistic effect of ML, a combination of ML and methotrexate was successfully tested using polymeric nanoparticles against the survival rate of triple-negative breast cancer cells. Methotrexate and polyethylene glycol–grafted chitosan polymeric nanoparticles were used. These polymeric nanoparticles were both glutathione and acid-sensitive to enable targeted delivery to cancer cells. These nanoparticles were spherical in transmission electron microscopy image and had a mean PS of 341.0±1.6 nm, ZP of 20.7±0.3 mV, and ML loading of 8.5%. It was observed that in a simulated tumor-endosome microenvironment medium containing high glutathione concentration and low pH, the ML release from nanoparticles was more than 68% within 8 h. Further, based on the release of methotrexate, it was demonstrated that the structure of the nanoparticles gets destroyed in the tumor-endosome microenvironment medium. Finally, a cell survival rate of 21.94±1.43% in MDA-MB-231 cells was produced by the ML and methotrexate-loaded nanoparticles whereas methotrexate alone was able to reduce the survival rate to a value of 43.66±1.77%.[115] Thus, the synergistic effect of ML in the anticancer effect was once again confirmed. However, there are still more research gaps in this area of the synergistic effect of ML with other cytotoxic agents. More elaborate research needs to be carried out in this regard.

Nanocomplexes

Nanocomplexes are slightly more advanced delivery systems to nanosuspension wherein a polymer is complexed physically or chemically with the drug. It can be considered different from polymeric nanoparticles (nanospheres) or nanocapsules in that the drug is not physically encapsulated within the polymer. Instead, it is attached or complexed to the polymer by means of hydrophobic interactions or hydrogen bonding. In the case of phenolic compounds such as ML, there is immense potential and possibility for the formation of nanocomplexes with proteins. This can enhance the bioavailability of poorly water-insoluble drugs.[116] The possibility of nanocomplexation of ML using peptone powder has been explored recently. It was observed that the nanocomplex of ML with peptone produced nanostructures (63.69-82.84 nm) with enhanced aqueous solubility of ML.[117] However, the studies of ML in the form of nanocomplex are still limited, and important aspects such as drug release, stability, biocompatibility, and pharmacokinetics are yet to be explored in detail. It is presumed that all these can depend on the types of polymer and the interaction between the ML and polymer.

Polymeric micelles

These nanostructures have a core-shell structure with a drug-loading hydrophobic core for the solubilization of poorly water-soluble drugs.[118] Further, it has a hydrophilic shell rendering it biocompatible. Solubility enhancement, controlled encapsulation, faster drug release, and desired biodistribution are some of the major opportunities for polymeric micelles to enhance the potential of ML.[119] Interestingly, acetal bonds containing ML forms polymeric micelles by self-assembling in aqueous media. These acetal bonds containing ML can act as a prodrug and is prone to acid hydrolysis to yield the ML. Such an approach has been tried to enhance the cytotoxic activity of ML against gastric cancer. The formed micelles were spherical and had a mean PS of 124.7 nm. Meanwhile, the ZP showed a pH-dependent value with increased ZP values at a lower pH of the medium, confirming the protonation of the nanomicelles in acidic media. Similarly, a pH-dependent ML release was also observed. At a pH of 6.0, 20% release was noted after 36 hr whereas it was around 80% at medium pH of 5.0. This indicated a good ML release at the acidic tumor microenvironment. Further, a minimal ML release at pH 7.4 indicated the physical stability of the polymeric micelles in the plasma. The cell line studies in SNU-5 and MKN45 cells confirmed the enhanced uptake of polymeric micelles of ML. Further, the MTT assay showed a concentration-dependent cytotoxic effect of polymeric micelles of ML. However, no tissue damages were produced which indicated the safety of this nanocarrier system. Meanwhile, extensive tumor necrosis was observed with the polymeric micelles of ML. The prolongation of circulation of polymeric micelles of ML was noted in a rat model. An increase in AUC, increase of MRT and half-life, and decrease in clearance were also noted as advantages of polymeric micelles of ML compared to pure ML.[120]

Mixed micelles

Mixed micelles are nanostructures that help to overcome the disadvantages of polymeric micelles with a single polymer in terms of stability, entrapment efficiency, drug loading, and narrow size distribution.[121] When mixed micelles of ML was prepared with Soluplus® and Poloxamer 188, a PS of 111.8 ± 14.6 nm, PI of 0.17 ± 0.02, ZP of −1.04 ± 0.12 mV, entrapment efficiency of 89.58 ± 2.54% and drug loading of 5.46 ± 0.65% were noted. However, the release of ML was less than that from pure ML and ML nanosuspension. The mixed micelles showed ML release of 59.6 and 68.2 % at pH 1.2 and 6.8, respectively after 24 hr. However, the mixed micelles showed higher transport across Caco-2 cell monolayers than its nanosuspension. Moreover, the mixed micelles showed higher AUC for ML than that from its nanosuspension.[105] In another study, mixed micelles of ML were prepared using Soluplus and Solutol® HS15 by organic solvent evaporation method. A PS of 80.41 ± 2.46 nm, PI of 0.074 ± 0.056, ZP of −0.139 ± 0.020 mV, entrapment efficiency of 98.37 ± 1.23%, and drug loading of 4.12 ± 0.16% were noted. In the same study, mixed micelles of ML were prepared using Soluplus and d-alpha-tocopheryl polyethylene glycol 1000 succinate by organic solvent evaporation method and a PS of 176.1 ± 3.85 nm, PI of 0.188 ± 0.054, ZP of −0.020 ± 0.012 mV, entrapment efficiency of 94.61 ± 1.52% and drug loading of 4.03 ± 0.56% were noted. The pharmacokinetics study after oral administration of these micelles revealed that mixed micelles significantly increase the C_{max} and half-life for ML in the blood. However, there was no significant difference in the T_{max} values. These mixed micelles also showed higher transport across Caco-2 cell monolayers than pure ML.[122]

In yet another study of mixed micelles with ML, Pluronic F127 and L61, a PS of 228.0±2.1 nm, PI of 0.298±0.012, ZP of −0.89±0.02 mV, entrapment efficiency of 81.57±1.49% and drug loading of 27.58±0.53% were observed. Moreover, the mixed micelles increased the transport across Caco-2 cell monolayers than pure ML. Moreover, a 2.83-times increase in relative oral bioavailability was observed compared to pure ML.[123] The study on the effects of lecithin in the mixed micelles containing sodium deoxycholate and Pluronic revealed some interesting facts. The inclusion of lecithin increased the hydrophobic region and thereby increased the entrapment efficiency of ML. Further mixed micelles with lower PS and PI are possible by the inclusion of lecithin. Further, it sustained the ML release from the system owing to the hydrophobic nature and prolonged the presence of ML in the systemic circulation of rats after intravenous administration. Further, a 3.41-times increase in the AUC of ML was observed compared to the administration of pure ML. The half-life of ML was also increased. Moreover, lecithin in the mixed micelles containing sodium deoxycholate produced a relative

bioavailability of 2.9 times for ML after oral administration. However, the presence of lecithin in the mixed micelles of Pluronic could not provide any satisfactory performance after oral administration in rats.[124]

Overall, it could be reasonably assumed that the solubilizers used in the above-mentioned mixed micelles are helpful in enhancing the solubility and permeability of ML. Further, the enhancement of pharmacokinetics is also possible by formulation of ML to mixed micelles using appropriate solubilizer combinations. Poloxamers are widely used for the formulation of mixed micelles of ML owing to the high binding capacity of these polymers with compounds containing aromatic rings such as ML.[125] In addition, the inclusion of some hydrophobic agents like lecithin can improve the formulation characteristics. However, exploring the causes of inability of lecithin to improve the bioavailability of ML from the mixed micelles of Pluronic would be interesting. Also, while the effect of mixed micelles on PS, PI, ZP, entrapment efficiency, and drug loading of mixed micelles have been reported, their effect on the stability of ML-loaded mixed micelles is yet to be studied in detail.

Supramolecular polymer assembly

Supramolecular polymers have recently gained much attention owing to their responsiveness to external stimuli. The possibility of self-healing, and environment-friendly nature is another advantage of such polymers.[126] Their ability to fast and precise response to environmental changes makes supramolecular polymers an attractive nanostructured and structurally-ordered delivery platform for therapeutic agents.[127] ML-loaded Supramolecular Polymer Assembly (SPA) comprising β-cyclodextrin, polypropylene glycol, and folic acid through host-guest interaction has been reported for thermo-responsive release. A PS of 76.6±3.1 nm and PI of 0.29±0.03 were observed in water for the supramolecular polymer assembly without loading ML. The ratio of ML:SPA had a significant role in PS, ZP, entrapment efficiency, and drug loading. Except entrapment efficiency, all other parameters were found to increase when the ratio of ML:SPA was changed from 0.5:1 to 1:1. The ML-loaded SPA (at a ratio of 1:1 for ML:SPA)showed a PS of 102±2.08 nm, ZP of 25.33±3.02 mV, entrapment efficiency of 21.78±3.3% and drug loading of 15.29 ±2.54% were observed. The entrapment efficiency was found to be determined by the host-gust interactions between β-cyclodextrin and polypropylene glycol. Interestingly, good structural stability of the ML-loaded SPA was demonstrated by unchanged PS even after 24 hr of storage. Furthermore, the hemolysis assay confirmed blood compatibility of the ML-loaded SPA. These SPAs demonstrated well-controlled drug release by thermo-trigger and active uptake into cancer cells with little adverse effect on normal cells.[128] Despite the promising results of these studies, it can be seen that the combined advantages of supramolecular assembly and the nanosize effect have not yet been explored to their full potential. Further extensive studies could open more possibilities and opportunities in this area.

In another supramolecular polymer assembly for the delivery of ML, supramolecular polymers with di-functional adenine-containing end groups were used. The spontaneous self-assembly of these supramolecular polymers in aqueous media resulted in nanospherical micelles. Further, adenine groups provided sufficient resistance to micelles towards salt concentrations. The mean PS of the blank nanospherical micelles was around 33 nm. Meanwhile, the mean PS of ML-loaded nanospherical micelles was 125±18.7 nm signifying the importance of ML on PS. Meanwhile, the ZP of the ML-loaded nanospherical micelles was 20.07±8.87 mV. A slight increase in ML release was observed when the pH of the release medium was changed from 7.4 to 6.0. Interestingly, ML-loaded nanospherical micelles showed a significantly faster ML release at mildly acidic pH (6.0 or 6.5) and 40°C than under the same pH values at 37°C. Thus, slightly acidic pH and higher temperature favored significant ML release from nanospherical micelles. Therefore, the simple approach of the addition of an adenine group showed good potential for the development of a superior tumor-targeted delivery system. The cell viability assay in RAW 254.7 cells at 37°C in pH 7.4 showed that the ML-loaded nanospherical micelles had minimal toxicity against normal cells under normal physiological conditions. However, significant toxicity was observed in HeLa cells at 37°C in pH 7.4 demonstrating a significant action of ML-loaded nanospherical micelles against tumor cells. Further, the cytotoxicity was higher in HeLa cells at 37°C and pH 6.0.[129] The developed system can be considered very potent against cancer cells and without harming normal cells. However preclinical studies are also needed for further confirmation of the in vivo performance of the proposed mechanism of the supramolecular polymer assembly using adenine groups. Furthermore, opsonization and the possibility of influence of the reticuloendothelial system resulting in the rapid clearance of the system can affect the proposed efficacy. Also, whether the degradation of the ML-loaded nanospherical micelles at the tumor microenvironment or its uptake will be the major mechanism can also decide the fate and performance of the system. Therefore, further studies in this regard may be necessary.

Liposomes

Liposomes are lipid-based drug vesicular DDSs with several advantages and some disadvantages. Outstanding characteristics of liposomes on encapsulated drugs include prevention of physiological degradation, prolonging the half-life, and regulating its release.[130] Further liposomes are biocompatible and safe. Additionally, by using passive or active targeting to deliver their payload only to the target site, liposomes can enhance the maximum tolerable dose, decrease systemic adverse effects, and enhance therapeutic advantages.[131] Moreover, due to the presence of both lipophilic and hydrophobic regions for drug loading, liposomes form a versatile system for plant-derived

phytochemicals.[132] Liposomes of honokiol, an isomer of ML with a similar structure, increased its solubility and stability.[75] Thus, it could be reasonable to expect such solubility and stability enhancement of ML by liposome formulation. Liposomes of ML have been studied with 1,2-dipalmitoyl-sn-glycero-3-phosphocholine and 1,2-diacyl-sn-glycero-3-phosphocholine and encapsulation efficiencies of 64.26±2.92 and 74.13±1.86, respectively was reported. The size of the liposomes increased with higher ML content. Furthermore, the addition of cholesterol reduced the size of liposomes with 1,2-diacyl-sn -glycero-3-phosphocholine by rendering more flexibility and fluidity. Moreover, these liposomes had significant inhibition on vascular smooth muscle cell proliferation.[133] Similarly, ML-loaded liposomes prepared separately with Distearoyl Phosphatidylcholine (DSP), Dipalmitoyl Phosphatidylcholine (DPP), and Dimyristoyl Phosphatidylcholine (DMP) also showed inhibition on vascular smooth muscle cell proliferation. The liposomes with DMP showed the lowest encapsulation efficiency of 67.19±2.92%. Meanwhile, the highest encapsulation efficiency was shown by DSP with a value of 84.87±1.97%. DPP showed an encapsulation efficiency of 75.05±3.93%. Interestingly, these values were found to be directly dependent on the acyl chain length, i.e., DMP(C14) < DPP(C16) < DSP(C18). The study further showed that an increase in the acyl chain length of the lipid increases the mean liposome size. Thus, DMP, DPP, and DSP had mean liposome sizes of 25.27 nm, 29.44 nm, and 39.59 nm. These liposomes had an inhibitory effect on vascular smooth muscle cell proliferation in the order DMP > DPP > DSP; once again dependent on the acyl chain length of the lipid. However, the liposome stability (and encapsulation efficiency) was in the order DSP > DPP > DMP.[134] These results implied the importance of the chain length of the lipid in the formulation of liposomes. Thus, the selection of acyl chain length could be one of the major factors to be considered in achieving an optimum liposome formulation of ML.

In another attempt, co-delivery of berberine and ML has been tried by formulating liposomes. Chondroitin sulfate-modified liposomes with berberine and ML molar ratio of 2:1 were evaluated on A549 cells to study their synergistic effect on lung cancer. These liposomes had a mean PS of 158.3±4.32 nm, PI of 0.196±0.062, ZP of -37.24±2.64 mV, ML entrapment efficiency of 91.72±0.99% and ML loading of 2.26±1.02%. Bcl-2, Bax, and Caspase-3-mediated apoptosis was found to be enhanced by the liposomes. Meanwhile, the IC_{50} value of ML on A549 cells at 48 h was 79.83 µM. Furthermore, the liposomes increased the plasma stability, prolonged the circulation time, increased *in vivo* targeting of berberine and ML, and enhanced tumor inhibition rate (81.48%) in A549-bearing nude mice.[135] These results are promising for future research on ML-loaded liposomes. However, the application of liposome formulation for the delivery of ML is yet to be explored for more therapeutic applications.

Lipid-polymer hybrid nanostructures

Burst release of drugs, leaking of drugs from the delivery system, lack of precision in drug release, stability problems, biocompatibility, toxicity, and absorption by the reticuloendothelial system are some of the disadvantages of lipid and polymeric nanostructures. Such disadvantages of both lipid and polymeric systems have been tried to overcome by the lipid-polymer hybrid nanostructures. The biomimetic potential of the lipid systems and mechanistic advantages of the polymeric systems can form synergistic systems, particularly useful in cancer chemotherapy.[136] Meanwhile, monolithic, polymer core-lipid shell, biomimetic lipid-polymer, hollow core-shell vector, and polymer-caged systems have been suggested for lipid-polymer hybrid nanostructures.[137] In an attempt with a lipid-polymer hybrid nanostructure, co-encapsulation of ML and gold nanoparticles has been demonstrated to prolong circulation. Polylactic-co-glycolic acid nanoparticles were surface-modified with trastuzumab. During co-encapsulation of gold nanoparticles, the polylactic-co-glycolic acid nanoparticles were surface-coated with D-α-tocopheryl polyethylene glycol 1000 succinate. These lipid-polymer hybrid nanostructures had a mean PS of 136.1±1.3 nm, PI of 0.109±0.009, ZP of −8.2 ±1 mV, and ML entrapment efficiency of 81.4±1.8%. The MTT assay in MCF-7 cells confirmed better activity of ML-loaded nanostructure than pure ML. Thus, the loading of ML to the lipid-polymer hybrid nanostructure lowered its IC_{50} from 2.92±0.32 to 1.81±0.02 µg/mL.[138] However, the feasibility of scale-up of the manufacturing of ML-loaded lipid-polymer hybrid nanostructures can be a challenge in achieving an industrially acceptable system. Also, due consideration is needed in enhancing stability and reducing chemoresistance during the development of such formulations of ML.

Metal-Organic Framework (MOF)

Metal-Organic Frameworks (MOFs) are versatile drug delivery platforms and are comprised of organic ligands and metal ions/ clusters through coordinative bonds.[139] Solubility and bioavailability improvement also have been demonstrated with the use of MOFs.[140] In such an attempt, Zr-based MOF had been successfully able to enhance the bioavailability of ML. In this reported study, ML was impregnated onto Uio-66(Zr) MOF. Interestingly, a time-dependent ML loading onto MOF was observed. The ML-MOF loading efficiency was highest at 36 hr with a loading efficiency of 72.16±2.15%. The loading of ML onto the MOF increased the mean PS from 338.90±18.42 to 500.80±16.63 nm. Thus, ML loading had a direct influence on PS. Meanwhile, the percent ML release was less than 5 in media pH of 2.0, 7.4, and 6.8 when tested for 5 hr. Further, acute oral toxicity studies of ML-MOF in female Sprague Dawley rats did not show death or toxicity. Finally, the oral bioavailability studies of ML-MOF in male Sprague Dawley rats confirmed enhanced bioavailability of ML from ML-MOF compared to that from pure

ML. After oral administration of ML-MOF at an ML dose of 100 mg/kg in rats, $AUC_{0-12\,h}$, $AUC_{0-\infty}$, T_{max}, C_{max}, and $T_{1/2}$ for ML were 1823±167.31 μg×min/mL, 2099.95±148.48 μg×min/mL, 196.97±17.38 min, 3.77±0.33 μg×min/mL, 206.21±27.95 min, respectively. Meanwhile, $AUC_{0-12\,h}$, $AUC_{0-\infty}$, T_{max}, C_{max}, and $T_{1/2}$ for ML after administration of pure ML were 823.3±139.10 μg×min/mL, 903.97±140.09 μg×min/mL, 55.77±4.17 min, 2.57±0.26 μg×min/mL, 100.00±20.40 min, respectively. Thus, significant increases in bioavailability and pharmacokinetic parameters were observed with ML-MOF compared to pure ML. However, no significant difference in tissue distribution was observed for ML-MOF compared to pure ML.[86] The same group in another report further demonstrated the application of this ML-MOF can significantly enhance the blood–brain barrier crossing of ML. Such an enhancement can increase the neuroprotective properties of ML by achieving higher concentrations in the brain. Initially, molecular docking and molecular dynamic simulations were carried out to confirm acceptable binding energies. Further, the *in vivo* studies to check the comparative effect of ML-MOF against pure ML were carried out by $AlCl_3$-induced neurotoxicity in a mice model. Interestingly, the ML-MOF showed improved neuroprotective activities. ML-MOF significantly inhibited neutrophil infiltration and reduced apoptotic neuronal counts. Moreover, ML-MOF demonstrated damage reversal compared to ML.[39] The application of MOFs for ML delivery seems promising from the available reports. Also, tremendous opportunities rest with MOF-based delivery systems. However, MOF-based systems also pose challenges such as insufficient stability in physiological medium, toxicity concerns of metal ions, and lack of adequate *in vivo* reports. Hence the future of MOF-based delivery systems of ML depends on how these challenges are addressed by more studies and evaluations.

Future prospects

The significant enhancement of the potentials of ML was observed with the above-mentioned reported DDSs. However, compared to other plant-derived bioactives such as curcumin, resveratrol, berberine, and quercetin, ML has not been tried with a variety of advanced DDSs. A typical example is the use of graphene oxide for enhancement of the effect of curcumin against breast cancer.[141] The importance of graphene and its derivatives in nanomedicine is well established and can be a suitable DDS for ML to explore.[142] Further, it has been observed that the metabolites of ML, ML-SUL, and ML-GLU have limited access to brain tissue. Hence, a nose-to-brain approach of ML would be imperative against conditions such as neurodegenerative diseases.[143,144] Meanwhile, co-processed excipients could be used for a plethora of desired applications using ML.[145] Like liposomes, niosomes also offer the advantages of enhancement of efficacy and lowering of toxicity of the phytoactive compounds.[146] Further modifications of the noisome are also a choice for the betterment of its performance.[147] Meanwhile, even though spherical crystallization is comparatively an older technique, it can be still useful for crystalline drugs with poor watersolubility.[148] Therefore, it can be considered for the solubility, dissolution, and bioavailability enhancement of ML. Similarly, a variety of basic and advanced forms of tablets and capsules are available for tailored therapeutic applications. Such an approach with ML is still unexplored. Carbon dots have tremendous advantages of high biocompatibility and low toxicity and have been explored in DDSs. Interestingly, in the case of carbon dots, they can be prepared using herbal medicines and can also be used to load phytoactive compounds.[149-151] Another technique, 3D printing, has been under tremendous use for exploring its potential in biomedicine and drug delivery. 3D printing can help the herbal drugs towards a personalized medicine for better therapeutic effect and patient compliance. Studies of 3D printing with herbal drugs are already underway.[152,153] Layered double hydroxide presents another class of advanced DDSs suitable for ML. The acidic nature of ML could be more helpful in loading into the layers of layered double hydroxide.[154] Curcumin has been successfully encapsulated in layered double hydroxide.[155] Such an approach would be feasible for ML also. The above-mentioned unexplored approaches (Figure 6) represent only a very few advanced DDSs that could be considered for ML. A lot many other DDSs are available for further tailoring any therapeutic application of ML, especially the anti-cancer effect.

CONCLUSION

ML has significant therapeutic applications with respect to anti-inflammatory, antioxidant, cardiovascular-protective, neuroprotective, and anti-cancer effects by multiple mechanisms through several cellular mediators. Meanwhile, the aqueous solubility of pure ML is only around 0.12 mg/mL and is sparingly soluble in aqueous buffers. However, ML has enhanced solubility at higher pH values due to phenolic groups. After oral administration, follows a first-order one-compartment model pharmacokinetics and ML-SUL and ML-GLU forms are the important metabolites. Among these, ML-GLU is the prominent metabolite of ML. The engineered ML crystals showed enhanced antibacterial effects on *Escherichia coli* and *Bacillus subtilis*. Meanwhile, solid dispersions enhanced the solubility and bioavailability of ML. However, scale-up and large-scale production could be a problem in solid dispersion for ML. The microstructures using mesoporous silica retarded ML release. However, limited studies in this area could not generate a solid conclusion about the effect of microstructures on ML delivery. Meanwhile, the reported nanostructures for ML significantly contributed to improving the activities of the ML compared to pure ML. Among these, supramolecular polymer assemblies of ML were highly successful. Liposomes, lipid-polymer hybrids, and MOFs were also successful in improving the efficacy of ML. Overall, it can be seen that advanced DDSs are successful in enhancing the therapeutic potential of ML to a significant level.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL STATEMENT

This study did not involve any animal or human experimentation.

AUTHOR CONTRIBUTIONS

SK: Writing - original draft, Visualization, Validation, Software, Resources, Investigation, Formal analysis, Data curation, Conceptualization, Funding acquisition. BAE, AAA: Writing - review & editing, Writing - original draft, Resources, Methodology, Investigation, Funding acquisition.HMA, SMB, ABN: Writing - review & editing, Resources, Conceptualization.

SUMMARY

This review outlines bioactivities, mechanisms, and clinical potential of ML, highlighting its anti-inflammatory, antioxidant, cardiovascular-protective, neuroprotective, and anti-cancer activities. It also covers biopharmaceutical aspects of ML, including solubility, dissolution, bioavailability, and pharmacokinetics, with a focus on solubility in various pH environments. The review examines the bioavailability and pharmacokinetics of pure ML following parenteral and oral administration, including single and multiple dose pharmacokinetics. It critically assesses advanced DDSs for ML, such as engineered crystals, solid dispersions, microstructures, and nanostructures. ML demonstrates significant therapeutic applications through multiple mechanisms involving various cellular mediators. Despite its poor aqueous solubility, ML's solubility improves in higher pH conditions due to its phenolic groups. After oral administration, ML follows first-order one-compartment model pharmacokinetics, with ML-SUL and ML-GLU as primary metabolites, the latter being more prevalent. Engineered ML crystals boost antibacterial effects against *Escherichia coli* and *Bacillus subtilis*, while solid dispersions enhance solubility and bioavailability of ML, though large-scale production remains challenging. Mesoporous silica-based microstructures slow ML release but lack sufficient research for definitive conclusions. Nanostructures, particularly supramolecular polymer assemblies, significantly improve activities of ML compared to pure ML, with liposomes, lipid-polymer hybrids, and MOFs also showing efficacy enhancements. In conclusion, advanced DDSs considerably augment therapeutic potential of ML.

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