Review Article

REVIEW ON OPTIMIZATION OF ORAL BIOAVAILABILITY OF PHYLANTHIN, ALIGNAN COMPONENT OF PHYLLANTHUS AMARUS SCHUM AND THONN USING NOVEL DRUG DELIVERY SYSTEM

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INTRODUCTION

Natural products, mainly plant-derived constituents, have long been sources of drugs. There are several advantages to using plants and phytoconstituents compared to pharmaceuticals available in modern medicine. Plants contain numerous classes of secondary metabolites, amongst; lignans considered being potential moiety with a wide spectrum of pharmacological activities. Lignans exist abundantly in the Phyllanthus species. (1)Phyllanthus amarus belongs to the family of flowering plants called Euphorbiaceae, this family found to have covered about 300 genera and around 7,700 species, disseminated in tropical and subtropical regions worldwide. (2)There is a lot of phyto compound extract in the plant, including, lignins, alkaloids, flavonoids, tannins, polyphenolic compounds and tetracyclic triterpenoids. (3) However, these constituents attribute to significant antidiabetic, hepatoprotective, immunosuppressant, anticancer, anti-inflammatory activities, among others. (1)Sequel to the importance of phyllanthin and related lignans, the interest in studying lignins compound more precisely phyllanthin, has significantly increased. However, Phyllanthus amarus identified to have contained a high amount of phyllanthin, (4) which was discovered to have poor oral absorption, due to its low water solubility. Scientists attempted to enhance oral bioavailability by employing different pharmaceutical techniques, like synthesizing nanoparticles, nanosuspension and microemulsion et al. (5) Previous studies have shown that the same concentration of nanoparticle formulation possesses better pharmacological activity compared with its raw drug. (6) Now a day, folk and scientific medicinal history of P. amarus thoughtfully integrated into the nano-technological considerations to get new therapeutic efficacies. (7)

Profile of Phyllanthin

According to the Dictionary of Natural Products 2011, Phyllanthin a bioactive lignin (Euphorbiaceae), possessed the following properties

Physicochemical properties

Synonyms: 3, 3, 4, 4, 9, 9, - hexamethoxylignan tetra – O – methyl secoisolaricresinal
Chemical name: 4 – [(2S, 3S) – 3 – [(3, 4 – dimethoxyphenyl) methyl] – 4- methoxy – 2- (methoxymethyl) butyl]- 1, 2- dimethoxybenzene

Key Words:
Phyllanthin, nanotechnology, harmonization, novel drug discovery, aliphatic drug, and native medicine.

ABSTRACT

Phyllanthus amarus is a widespread tropical plant, used for many years as the native medicine, which was found to be effective against many ailments. Researchers found the plant to be a rich source of Phyllanthin, a lignin compound isolated from the areal part of the plant, which known to be the biochemical marker of Phyllanthus amarus. Phyllanthin found effective against diabetics, liver abnormalities, cancer, et al. it was reported to exhibiting low oral bioavailability due to poor water solubility. Therefore, there is a need to optimize oral bioavailability of the compound using novel drug delivery system in order to develop aliphatic drugs for better health care. The study focused on studying various options adopted to enhance the oral bioavailability of Phyllanthin and to open a gateway for novel drug discovery. The research summarized articles published in various journals of publications for the past two decades. The study concluded that, various techniques of a novel drug delivery system found to be an option to enhance the therapeutic efficiency of Phyllanthin upon oral administration.
Recent approaches to enhance oral absorption and bioavailability of Phyllanthus amarus Schum and Thonn

Isolation of Phyllanthin compound from Phyllanthus amarus Schum and Thonn

Sandeep et al. (2013) isolated (1.23%) yields of Phyllanthin from the aerial parts of Phyllanthus amarus using silica gel column chromatography techniques by employing hexane-ethyl acetate as a solvent mixture to make gradient elution. The Phyllanthin crystals purified using recrystallization method and acetate as a solvent mixture to make gradient elution. The column chromatography techniques by employing hexane from the aerial parts of Phyllanthus amarus using Sandeep Schum and Thonn Isolation of Phyllanthin compound from Phyllanthus amarus

Molecular Structure

![Molecular structure of Phyllanthin](image)

**Figure 1** Structure of Phyllanthin

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C24H34O6</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>418.529g/mol</td>
</tr>
<tr>
<td>Log p</td>
<td>3.2</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in organic solvent</td>
</tr>
<tr>
<td>Melting point</td>
<td>96 °C</td>
</tr>
<tr>
<td>Density</td>
<td>1.069</td>
</tr>
<tr>
<td>Storage condition</td>
<td>Light resistance and tight close container</td>
</tr>
</tbody>
</table>

**Isolation of Phyllanthin compound from Phyllanthus amarus Schum and Thonn**

Sandeep et al. (2013) isolated (1.23%) yields of Phyllanthin from the aerial parts of Phyllanthus amarus using silica gel column chromatography techniques by employing hexane-ethyl acetate as a solvent mixture to make gradient elution. The Phyllanthin crystals purified using recrystallization method and it found to have gain purity of “more than 98%”. However, the researchers using UV, IR, MS, H- NMR, and C- NMR spectra identified the Phyllanthin compound.

Nguyen Duc et al. (2014) also employed the techniques of “scanning calorimetry, thermogravimetric analysis, and X-ray crystallography” to establish physicochemical properties of phyllanthin, amongst PH – solubility, ionization property, and lipophilicity. The results indicated that phyllanthin crystals had a melting point and melting enthalpy range of 96.67–97.03 °C and 109.61–116.34 J/g, respectively.

Synthetic nanoparticles: Silver nanoparticles synthesized by manipulation of the properties of silver metal that prevailed to have an excellent broad-spectrum antibacterial property. Henceforward, researchers employ the use of synthetic nanoparticles, more precisely silver nanoparticles (AgNPs) to overcome the advent of Multi-Drug Resistance bacteria. A study conducted by J. Prakash Yadav (2014), concluded that, synthesized silver nanoparticles from P. amarus extract have a good antibacterial effect against multidrug-resistant strains of P. aeruginosa. N.P.S. Acharyulu. 2014, concluded that, biosynthesized CuO nanoparticles of Phyllanthus amarus leaf extract possessed a potential antibacterial effect against both Gram-positive and Gram-negative bacteria as well as multidrug-resistant bacteria, but gram-positive bacteria found to be more sensitive to the formulation.

Nanosuspension: According to Himanshu et al., 2019 experiment, nanosuspensions can be formulated either by using a wet mill, a high-pressure homogenizer, emulsion solvent evaporation, melt emulsification method, or supercritical fluid technique, by employing additives like organic solvents, stabilizers, buffers, salts, polyols, osmogenes, cryoprotectant, and no matrix system required. Nanosuspension technique provided the most suitable alternative to enhance oral bioavailability of hydrophobic drugs. The solid-state of the drug offers solutions to issues of chemical stability, and the small size confers increased physical stability with respect to sedimentation. A study carried out by Pandey, Himanshu, 2013, compared the hepatoprotective effect between the crude extract P. Amarus and nanosuspension on paracetamol-induced acute hepatic injury rats. The study concluded that, the oral dose of crude extract of Pyllanthus Amarus requires to exhibit the same hepatoprotective effect, is five times higher than that of nanosuspension extract. This implies that, the problem of water insolubility, and irrational dosing among other herbal medicines, can be overcome using nanosuspension system. Previous studies evidenced that, nanoparticle formulation of particular herbal extract of the same concentration, elicited greater therapeutic activity compared to crude extracts formulation.

Nano-emulsion: Nanoemulsion prepared by spontaneous emulsification method, higher solubilization of drug molecules could be achieved by using proper oils, surfactants, and suitable hydrophilic-lipophilic balance (HLB) value. Selection of oils and surfactants, along with their suitable hydrophilic-lipophilic balance (HLB) value. This makes it to be an ideal technique adopted to enhance the solubility and bioavailability of water-insoluble drugs, due to this effect, the system gains high momentum in research field. In an in vivo study conducted by V. Deep et al. 2012, demonstrated on carbon tetrachloride CCl4 and galactosamine induced hepatotoxic adult rats. Surprisingly, the study discovered a dose of the hepatotoxic effect of nanotized extract of P. amarus (20mg/kg body wt.) is 5 times lower than that of non-nanosized extract (100mg /kg body wt.) and concluded that nano-emulsification method can be an alternative means to reduce dosage, dosing time and oral bioavailability of poor water soluble of herbal ethanoic extract.
achieved property because of gentle agitation and dilution of aqueous phases caused by digestive motility of the stomach and intestine, upon oral administration of the formulation. This theory evidenced by an in-vivo study conducted by Carvajal MT et al (2013) studying isolated lumen of the gut (22)Nguyen Duc et al. 2013 study demonstrated that, “Phyllanthin-SMEDDS could be fully emulsified within 6 min and formed fine micro-emulsions, with an average drop range of 27-42 nm”. The study further found that the release of phyllanthin from SMEDDS-capsule was considerably faster than that of conventional phyllanthin-capsule regardless the pH of dissolution media and it can maintain stability for at least 6 months upon storage under recommended condition (23). SMEDDS formulations confirmed to be an alternative to overcome the effect of poor oral bioavailability of traditional drugs. (24)

**Formulation of liposomes:** Liposomes are synthetic vesicles comprising aqueous core enclosed by one or more phospholipid bilayers, enable to lodge water and lipid-soluble molecules. Liposomes designed to deliver drugs, genes, and vaccines, and formulated in the form of conventional and polyethylene glycated (PEGylated) liposomes, in the pharmacokinetic study conducted by T. Parveen et al. (2016). The study proved evidence of enhancement in oral bioavailability and low dosing of lignin-loaded liposomes against conventional formulation. (26)

**Figure 3 Types of liposomes formulations**

Formulation of phytosomal complex tablet:Phytosomal tableting technology is a novel complex prepared by bounding the bioactive compound with phospholipids (natural or synthetic) through a polar end. It acts by producing small cells comprising aqueous core enclosed by on bilayer. It enables to lodge water and lipid-soluble molecules. Liposomes designed to deliver drugs, genes, and vaccines; et al. (25) bioactive lignans (phyllanthin and hypophyllanthin) formulated in the form of conventional and polyethylene glycated (PEGylated) liposomes, in the pharmacokinetic study conducted by T. Parveen et al. (2016). The study proved evidence of enhancement in oral bioavailability and low dosing of lignin-loaded liposomes against conventional formulation. (26)

**CONCLUSION**

The present study identified novel drug delivery systems used to enhance oral bioavailability, reduce dosing, minimize the chance of toxicity and increase the therapeutic efficiency of the lead molecule (Phyllanthin). However, studying pre-clinical parameters of the lead molecule will aid the novel drug discovery.

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**Area of Conflict:** The author declares no conflict of interest.


