

Phytosomes: Modern Approach to the Delivery of Herbal Drugs

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Abstract: Medicinal plants and their phytochemicals are now a fantastic remedy for a variety of illnesses. However, their clinical applicability may be limited due to their poor selectivity and bioavailability. In order to increase the bio-efficacy of dietary phytochemical transport, bioavailability is regarded as a significant problem. Various techniques for producing efficient carrier systems to increase the bioavailability of phytochemicals have been put forth. One of the more promising options for delivering insoluble phytochemicals is the use of nano-vesicles. The scientific literature has endorsed the widespread use of bilayer vesicles due to their versatility and ease of fabrication. Phytosome technology and its applications are introduced in the first section of the review, with a focus on formulation and characterization concepts.

Keywords: Phytosome, Phospholipid, Phytoconstituents, Phosphatidylcholine, Novel Drug Delivery System, Herbal extract

I. INTRODUCTION

Bioavailability can be increased via innovative medication delivery methods.[1 During the course of therapy, a revolutionary drug delivery system aims to release the medication at a rate that is based on the body's demands while delivering the active component to the site of action.[2]

Liposomes, niosomes, transferosomes, and pharmacosomes are some of the new vesicular drug delivery systems that have been developed for targeted and regulated drug delivery. Advances in vesicular drug delivery have made it possible to develop systems that allow for the targeting of drugs and the controlled or extended release of conventional pharmaceuticals. A phytosome is formed when the plant extract or its constituents attach to phospholipids.[3]

For millennia, people have employed a range of therapeutic approaches to preserve their health, including traditional medical procedures and phytomedicines. A contemporary attempt to properly control human ailments is the development of herbal medication delivery. Herbal remedies are being used for self-administration in every nation as a way to get healthcare that is outside the traditional purview of modern medicine. Water-soluble molecules make up the bulk of phytomedicine's bioactive ingredients, whilst the remaining ones are water-insoluble. Nevertheless, the effectiveness of phytoconstituents is limited due to their poor absorption when taken internally or topically[4] Numerous techniques, including as structural modification and the inclusion of solubility and bioavailability enhancers, have been found to increase the oral bioavailability of medications.[5]

Phytosomes:

Medicinal plants and their active ingredients have been used to cure a variety of illnesses for many years. The following are the main causes of the rise in the usage of herbal medications:[1-5]

- 1) Not all human diseases can be effectively cured by modern medicine.
- 2) Concerns over the safety and assurance of synthetic pharmaceuticals are growing and
- 3) A number of natural items have been demonstrated to outperform synthetic drugs without causing negative side effects.[11]

However, the therapeutic use of many plants active substances is debatable because of their limited oral bioavailability. [12-13] These components' low lipid solubility, large molecular weight, and presence of multi-ring polyphenols in their structures might all contribute to their poor absorption rate. [17-18]

Numerous strategies, including the development of emulsions [17], liposomes [18], and nano-formulations [19]; altering molecular structure; [20] and the administration of prodrugs, [21] have been put forth to address these issues. Out of all the methods, phyto-phospholipid complexes, or phytosomes, appear to be the most successful in boosting their bioavailability. [14]

Whereas "some" means cell-like, "phyto" refers to the plant. Herbosomes or phytosomes are soluble medications that improve absorption through the vesicular drug delivery mechanism. low-bioavailability Plant extracts and phosphatidylcholine (or any hydrophilic polar head group) react to form phytosomes, which are complexes of phospholipids and naturally occurring active phytochemicals bonded in their structures. [17]

When compared to common preparations, these formulations show better pharmacological and pharmacokinetic characteristics. The hydrophilic phytoconstituent-choline complexes are entirely covered by the lipid-soluble phosphatidyl part. High drug encapsulation, a higher stability profile (chemical bonds are established between the phytoconstituent and the polar head of the amphiphile molecule), and improved bioavailability are just a few of the amazing advantages of phytosomes. Furthermore, for polar phytoconstituents as well, a faster rate of absorption results in a lower dosage of active ingredients needed to have a biological impact. [17]

II. PRINCIPLE

A phytosome is created by combining a standardized extract or polyphenolic component with a stoichiometric quantity of the phospholipid in a non-polar solvent. The extracts' phytochemical constituents, flavonoids and terpenoids, enable their direct complexation with phosphatidylcholine. The bifunctional phosphatidylcholine molecule is composed of the hydrophilic choline moiety and the lipophilic phosphatidyl. The body and tail of the lipid-soluble phosphatidyl part encapsulate the choline-bound material, whereas the choline head of the phosphatidylcholine molecule attaches to phytocomponents. As a result, the phytoconstituents and phospholipid combine to create a lipid-compatible molecular complex called the phyto-phospholipid complex. [3]

The decreased absorption and bioavailability of polyphenolic components can be attributed to two main factors. These primary constituents are not too small to be absorbed by the diffusion process and are made up of several ringed molecules. The second reason is because flavonoid molecules, which make up the majority of polyphenols, are less soluble in lipids. Their absorption across cellular membranes is restricted by these constraints. [20]

Structure of Phytosomes:

For the first time, it was reported by Bombardelli et al. that phospholipids and molecules of flavonoid vegetal derivatives form a chemical link. [28] The molecular docking model for the interaction of 20(S)-protopanaxadiol (PPD) phospholipid complexes was studied by Pu et al. in 2016. The findings showed that two hydrophobic arms of the phospholipid molecule surrounded the hydrophobic portion of the PPD framework, while one of the hydrophilic OH groups formed a hydrogen bond with the phospholipid backbone of the P=O section. According to numerous publications, the primary contacts in phytosome vesicles are hydrogen interactions. The affinity of phospholipids for polyphenols results in the formation of upramolecular adducts with a certain stoichiometry, which may be determined using thermal analysis. [29]

Semalty et al. experimented with this parameter and discovered that the interaction between the two molecules was the cause of hydrophobic interactions or hydrogen bond formation. The formation of a hydrogen bond between the polar head and the polar functions of the active ingredient is the responsibility of the phospholipid-active ingredient. In conclusion, polyphenols' hydroxyl groups can successfully interact with phospholipids' nitrate and phosphate groups. [30]

III. PROPERTIES

Biological properties:

a) Phytosomes increase the active compounds' total bioavailability and active absorption when taken orally.

- b) Compared to traditional herbal remedies, phytosomes have a better pharmacokinetic profile.
- c) These herbal medicines work better and are more inventive than traditional herbal extracts.[20]

Physiochemical properties:

- a) Standardized plant extracts are used as the substrate and a stoichiometric amount of phospholipid is reacted to produce phytosomes. The polar head of the phospholipid and the polar functions of the substrate establish a hydrogen bond, which facilitates interaction between the two.
- b) Phytosomes take on a liposome-like micellar shape when they come into contact with water, and photon correlation spectroscopy (PCS) shows that they have acquired these liposomal structures.
- c) The size of phytosomes varies from 50 nm to several hundred meters.
- d) The fatty chain in both free and complex phospholipids emits the identical signals, according to data from the H1 NMR and C13 NMR. This demonstrates that the lipophilic active component is enclosed in long aliphatic chains.[3]

IV. PREPARATION METHOD

1.Using the solvent evaporation approach, precisely weigh the cholesterol and phospholipid, dissolve them in 10 milliliters of chloroform, and then sonicate the mixture for ten minutes with a bath sonicator. Solvent removal can be achieved by subjecting it to reduced pressure in a rotary evaporator set at 40°C. Once the solvent has been totally eliminated and the drug's polyphenolic extract has been hydrated, a thin layer is formed in a rotary evaporator. The phospholipid mixture was sonicated in an ice bath to dissipate heat. The prepared phytosome was stored in an amber-coloured bottle. [20]

2.To make phytosome vesicles, a thin layer rotary evaporator vacuum technique was employed. The herbal extract, phospholipid, and anhydrous ethanol were mixed in a 250 ml round-bottom flask that was attached to a rotary evaporator. When the solvent evaporates at a temperature of about 60°C, a thin film will form around the flask. In the phosphate buffer, the lipid layer will separate, forming a suspension of vesicles. The phytosomal suspension was subjected to 60% amplitude probe sonication.

The phytosomal suspension will be refrigerated for 24 hours before to characterization.[20]

3.Phytosomes can be produced by the reflux approach.

Phospholipid and polyphenolic extract were added to a 100 mL round-bottom flask with an internal temperature limit of 40°C, and the mixture was refluxed with dichloromethane (DCM) for an hour. After the solution evaporated, 15 millilitres of n-hexane were added until a precipitate formed. The precipitate was moved into a desiccator.[20]

4.Accurately weigh the phospholipid and polyphenolic extract. It should be put in a 100 ml round-bottom flask, refluxed with 30 mL of dichloromethane (DCM) for three hours at 60 °C, then diluted to 5–10 mL and mixed continuously with 30 mL of n-hexane to produce a precipitate. Collect the precipitate and store it in a vacuum desiccator for the night. After that, the precipitate is kept in an amber-coloured container that is tightly sealed.[20]

5.Five millilitres of dichloromethane (DCM) were added after phospholipid or soy lecithin and polyphenolic extract were mixed in equal amounts. Until the DCM evaporated, the mixture was agitated. While the thin film was still being agitated, 5 mL of n-hexane was added, and it was then entirely extracted within a fume hood.

After being hydrated, the thin film was sonicated to create the proper phytosomal complex. [20.]

V. DOSAGE FORM

Depending on its capacity to boost the bioactive component's efficacy and efficiency, an appropriate formulation or dosage form for the distribution of one can select phytosomes. The final formulation must consider the degree of biodegradability and tonicity, the size and release profile of the product needed, the surface characteristics of systems like permeability and charges, and the inherent qualities of herbal drugs like hydrophilicity or hydrophobicity. There are phytosome preparations that are topical and oral. Examples of therapeutic dosage formulations for phytosome delivery are shown here.[3]

A] Tablet:

Due to the phytosome complex's limited flow, sticky character, and low apparent density, a direct compression method is only appropriate for lower unitary doses. To create tablets with the required properties, the phytosome complex

should be diluted with 60–70% excipients. Wet granulation should be avoided since heat and water negatively impact the stability of the Phyto-phospholipid complex.[3]

B) Capsule:

The phytosome can be dissolved in oily medium (vegetable or semi-synthetic oil) to make a suspension that is then packed into the shell to produce soft gelatin capsules. 2 Hard gelatin capsules can be filled with phytosomes. Because precompression can change the disintegration time during a straight volumetric filling procedure, it is not required. The maximum amount of powder that may be placed in a capsule (often no more than 300 mg per size capsule) seems to be limited because of the low density of phytosomes. By employing a piston pump during the capsule filling procedure, we can enhance the quantity of powder that is placed into the capsules.[3]

C) Gel:

Add the phytosomal complex to the prepared emulsion or dispersion.[3]

VI. EVALUATION

1. Calculation of percentage yield:

The following formula was used to determine the phytosome complex's percentage yield:[21]

The percentage yield is calculated as follows:

$$\frac{\text{(practical yield)}}{\text{(theoretical yield)}} \times 100$$

2. Determination of entrap efficiency : [20]

The drug phytosomal complex is centrifuged for 90 minutes at 4°C at 10,000 rpm to separate the phytosome from the free drug, which is how the entrapment efficiency is determined. Calculate the amount of free drug present using UV spectroscopy.5.

The proportion of drug entrapment can be calculated using the formula.

$$\text{entrapment efficiency (\%)} = \frac{\text{(Total amount of drug)} - \text{(amount of free drug)}}{\text{(Total dosage of medication)}} \times 100$$

3. Particle size determination: [20]

At a given scattering angle of 90°, the average diameter of the phospholipid complex was measured using a Nanophox. [6]

4. Zeta potential:

The zeta sizes of the phytosomal complex are measured using Malvern Zeta sizer. [20]

5. Scanning electron microscopy (SEM): SEM was used to evaluate the particle's size and appearance.[20]

On the gold-coated brass stub of the electron microscope (JEOL JSM-6360 Scanning Microscope), a dry sample was mounted. Digital pictures of the phytosome complex were obtained by randomly scanning the stub at magnifications of 1000x, 5000x, 100,000x, and 30,000x.

6. Differential Scanning Calorimetry (DSC) :

Phosphatidylcholine, a physical mixture of drug extract and phosphatidylcholine, drug-phospholipid complex, and drug polyphenolic extract were all added to an aluminum cell and heated to 400°C at a rate of 50–250°C per minute in a nitrogen atmosphere using differential scanning calorimetry (DSC). An analyzer was used to record the peak transition onset temperatures.[20]

7. Drug content determination:

The drug concentration of the molecule was determined by accurately dissolving 100 mg of the phytosome complex in 10 ml of solvent.

The drug content was determined using a UV spectrophotometer and the dilution absorbance.[21]

8. FTIR:

The phospholipid structure and chemical stability of the medication will be investigated using FTIR analysis. To produce pellets, potassium bromide will be used to crush the phytosomal drug at a pressure of 600 kg/cm². There will be a scanning range of 4000 400cm⁻¹. [20]

9. Transition electron microscopy (TEM):

Using TEM at 1000x magnification, the size of phytosomal vesicles was assessed. [20]

10. solubility test:

To test for solubility, put 10 milliliters of solvent in glass containers. The liquid was centrifuged for 15 minutes after being agitated for 24 hours on a rotator shaker to remove excess extract. The supernatant was filtered using a membrane filter. Following that, dilutions were created using 1 ml of filtrate and 9 ml of an appropriate solvent. UV spectrophotometer analysis was performed, and the absorbance of concentration was calculated using a calibration curve.[22]

11. X-ray:

X-ray diffraction is currently used to analyze the microstructure of different amorphous and crystal materials. Phosphatidylcholine and phosphatidylcholine-phytophospho lipid complexes are commonly used for X-ray diffraction. Strong crystalline peaks that indicate a high crystal form are visible in the X-ray diffraction of an active component and physical combination. However, the lack of a crystalline peak in phyto-phospholipid complexes with active components indicates that the constituents in these complexes have an amorphous or molecular structure. [23]

12. Research on stability

The optimized formulation's physical stability was examined for six months under three distinct circumstances. Stability tests were carried out at low temperatures (4 °C), room temperature (28 °C), and high temperatures (40 °C).[25]

VII. ADVANTAGES

- A stronger chemical connection with lipid gives phytosomes more stability.[20]
- Phytosomes improve absorption through the skin because lipid layer.[20]
- A platform for the administration of a wide range of medications (protein molecules, peptides).[3]
- Secondly, the vesicular system is non-invasive and passive.[3]
- In phytosome technology, phosphatidylcholine, a crucial component of the cell membrane, serves as a carrier and improves the absorption of active ingredients, lowering the dosage. [3,20]

VIII. CONCLUSION

The technology known as phytosomes is patented. Phytosomes have the ability to go from hydrophilic environments to enterocyte cells' lipid-friendly environments membrane, then into the cell, and finally into the blood.²⁶ Phytoconstituents have a restricted solubility and are susceptible to degradation. The remarkable trapping ability, biocompatibility, and safety of vesicular drug delivery systems help to improve these attributes.²⁷ Vesicles have shown great promise as cellular delivery vehicles for a range of advantageous phytochemicals. Phytosomes are vesicular drug carriers that, through a complex between phytochemicals and phospholipids, enhance the absorption and bioavailability of bioactive molecules as well as the stability of compounds in general. Phytomedicine has been used extensively since ancient times and continues to this day. Phytosomes are a promising technique for delivering herbal medications in a more modern and efficient manner.

As the number of newly identified phytochemicals increases, studies on their potential medical uses in biological settings will be updated. However, the use of these molecules in food and pharmaceutical products is limited by their low solubility and sensitivity to degradation. At this point, improving these features might be possible with knowledge of vesicular drug delivery systems.

Because of their exceptional trapping capability, biocompatibility, and safety, vesicles have been demonstrated to be very promising delivery methods for a variety of advantageous phytochemicals at the cellular level. Phytosomes are

vesicular drug carriers that combine phytochemicals with phospholipids to form a complex. This complex improves the absorption and bioavailability of bioactive compounds as well as the stability of the compound as a whole.

The most popular nanocarriers for phytochemicals are liposomes, transfersomes, niosomes, and ethosomes. These nanocarriers differ in their size, release efficiency, and preferred target (e.g., transfersomes and ethosomes for topical treatment). The transport of plant-based nutraceuticals has been further enhanced by the invention of nano-phytosomes, one of the newest lipid-based vesicles with reduced dimensions. Physical measurements that provide information on release kinetics and formulation stability must be analyzed in order to adequately define each formulation, guarantee a good safety profile, and satisfy repeatability requirements.

REFERENCES

- [1]. Lu M, Qiu Q, Luo X, et al. Phyto-phospholipid complexes (phytosomes): a novel strategy to improve the bioavailability of active constituents. *Asian J Pharm Sci.* 2019;14(3):265–274. doi:10.1016/j.ajps.2018.05.011
- [2]. Ittadwar PA, Puranik PK. Novel umbelliferone phytosomes: development and optimization using experimental design approach and evaluation of photo-protective and antioxidant activity. *Int. J. Pharm. Pharm. Sci.* 2017;9:218–28.
- [3]. Pawar HA, Bhangale BD. Phytosome as a novel biomedicine: a microencapsulated drug delivery system. *J Bioanal Biomed.* 2015 Jan 1;7(1):6–12.
- [4]. Sindhumol PG, Thomas M, Mohanachandran PS. Phytosomes: a novel dosage form for enhancement of bioavailability of botanicals and nutraceuticals. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2010;2(4):10–4.
- [5]. Amudha S, Prabal KM, Jeganathan NS. Evaluation of anti diabetic activity of *Syzygium cumini* extract and its phytosome formulation against streptozotocin-induced diabetic rats. *The Pharma Innovation Journal.* 2018;7:603–8.
- [6]. Lu M, Qiu Q, Luo X, et al. Phyto-phospholipid complexes (phytosomes): a novel strategy to improve the bioavailability of active constituents. *Asian J Pharm Sci.* 2019;14(3):265–274. doi:10.1016/j.ajps.2018.05.011
- [7]. Raeiszadeh M, Esmaili-Tarzi M, Bahrapour-Juybari K, et al. Evaluation the effect of *Myrtus communis* L. extract on several underlying mechanisms involved in wound healing: an in vitro study. *S Afr j Bot.* 2018;118:144–150. doi:10.1016/j.sajb.2018.07.006
- [8]. Poursalehi HR, Fekri MS, Far FS, et al. Early and late preventive effect of *Nigella sativa* on the bleomycin-induced pulmonary fibrosis in rats: an experimental study. *Avicenna J Phytomed.* 2018;8(3):263.
- [9]. Oloumi MM, Vosough D, Derakhshanfar A, et al. The healing potential of *Plantago lanceolata* ointment on collagenase-induced tendinitis in burros (*Equus asinus*). *J Equine Vet Sci.* 2011;31 (8):470–474. doi:10.1016/j.jevs.2011.03.014
- [10]. Samareh-Fekri M, Poursalehi HR, Mandegary A, et al. The effect of methanol extract of fennel on bleomycin-induced pulmonary fibrosis in rats. *J Kerman Univ Medical Sci.* 2015;22(5):470–483.
- [11]. Bhise JJ, Bhusnure OG, Jagtap SR, Gholve SB, Wale RR. Phytosomes: a novel drug delivery for herbal extracts. *J Drug Deliv Ther.* 2019;9(3–s):924–930.
- [12]. Teng Z, Yuan C, Zhang F, et al. Intestinal absorption and firstpass metabolism of polyphenol compounds in rat and their transport dynamics in Caco-2 cells. *PLoS One.* 2012;7(1):e29647. doi:10.1371/journal.pone.0029647
- [13]. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr.* 2004;79(5):727–747.
- [14]. Bhattacharya S. Phytosomes: the new technology for enhancement of bioavailability of botanicals and nutraceuticals. *Int J Health Res.* 2009;2(3):225–232. doi:10.4314/ijhr.v2i3.47905
- [15]. Kidd P, Head K. A review of the bioavailability and clinical efficacy of milk thistle phytosome: a silybin-phosphatidylcholine complex (Siliphos). *Altern Med Rev.* 2005;10(3):193–203.

- [16]. Ting Y, Jiang Y, Ho C-T, et al. Common delivery systems for enhancing in vivo bioavailability and biological efficacy of nutraceuticals. *J Funct Foods*. 2014;7:112–128. doi:10.1016/j.jff.2013.12.010
- [17]. Lu W, Kelly AL, Miao S. Emulsion-based encapsulation and delivery systems for polyphenols. *Trends Food Sci Technol*. 2016;47:1–9. doi:10.1016/j.tifs.2015.10.015
- [18]. Munin A, Edwards-Lévy F. Encapsulation of natural polyphenolic compounds; a review. *Pharmaceutics*. 2011;3(4):793–829. doi:10.3390/pharmaceutics3040793
- [19]. He J, Luo L, Zeng L. Recent advances in research on preparation technologies and applications of tea polyphenol nanoparticles. *Food Sci*. 2011;32:317–322. <https://doi.org/10.2147/IJN.S318416> DovePress 7012 International Journal of Na
- [20]. Kumar A, Kumar B, Singh SK, Kaur B, Singh S. A review on phytosomes: novel approach for herbal phytochemicals. *Asian J Pharm Clin Res*. 2017;10(10):41-7
- [21]. Singh RP, Narke R. Preparation and evaluation of phytosome of lawsone. *International Journal of Pharmaceutical Sciences and Research (IJPSR)*. 2015;6(12):5217-26.
- [22]. Gahandule MB, Jadhav SJ, Gadhave MV, Gaikwad DD. Formulation and development of hepato-protective *Butea monosperma* -phytosome. *Int J Res Pharm Pharm Sci*. 2016;1(4):21-7.
- [23]. Lu M, Qiu Q, Luo X, Liu X, Sun J, Wang C, Lin X, Deng Y, Song Y. Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. *Asian journal of pharmaceutical sciences*. 2019 May 1;14(3):265-74.
- [24]. J Anar Patel, P Anu. Herbosome: An approach to deliver *Lagerstroemia speciosa* extract: formulation, characterization and stability study. *International Journal of Recent Scientific Research*. 2022 April;13 (C): 961-966.
- [25]. Anwar E, Farhana N. Formulation and evaluation of phytosome-loaded maltodextrin-gum Arabic microsphere system for delivery of *Camellia sinensis* extract. *Journal of young pharmacists*. 2018;10(2s):S56.
- [26]. Karole S, Gupta GK. Preparation and evaluation of phytosomes containing ethanolic extract of leaves of *Bombax ceiba* for Evaluation. 2019;6(2):1-5. hepatoprotective activity.
- [27]. Barani M, Sangiovanni E, Angarano M, Rajizadeh MA, Mehrabani M, Piazza S, Gangadharappa HV, Pardakhty A, Mehrbani M, Dell'Agli M, Nematollahi MH. Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. *International Journal of Nanomedicine*. 2021;16:6983.
- [28]. Bombardelli E, Curri SB, Della Loggia R, et al. Complexes Between Phospholipids and Vegetal Derivatives of Biological Interest. *Fitoterapia*. 1989;60:1–9.
- [29]. Pu Y, Zhang X, Zhang Q, et al. 20(S)-protopanaxadiol phospholipid complex: process optimization, characterization, in vitro dissolution and molecular docking studies. *Molecules*. 2016;21 (10):1396. doi:10.3390/molecules21101396.
- [30]. Semalty A, Semalty M, Rawat MSM, et al. Supramolecular phospholipids–polyphenolics interactions: the PHYTOSOME® strategy to improve the bioavailability of phytochemicals. *Fitoterapia*. 2010;81(5):306–314. doi:10.1016/j.fitote.2009.11.001
- [31]. Baron G, Altomare A, Regazzoni L, et al. Profiling *Vaccinium macrocarpon* components and metabolites in human urine and the urine ex-vivo effect on *Candida albicans* adhesion and biofilm formation. *Biochem Pharmacol*. 2020;173:113726
- [32]. Riva A, Ronchi M, Petrangolini G, Bosisio S, Allegrini P. Improved oral absorption of quercetin from quercetin phytosome®, a new delivery system based on food grade lecithin. *Eur J Drug Metab Pharmacokinet*. 2019;44(2):169– 177. doi:10.1007/s13318-018-0517-3
- [33]. Mollace V, Scicchitano M, Paone S, et al. Hypoglycemic and hypolipemic effects of a new lecithin formulation of bergamot polyphenolic fraction: a Double Blind, Randomized, PlaceboControlled Study. *Endocr Metab Immune Disord Drug Targets*. 2019;19(2):136–143. doi:10.2174/1871530319666181203151513