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THE POTENTIAL ENCAPSULATION OF EUPHORBIACEAE PLANT EXTRACTS: A REVIEW

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ABSTRACT

Encapsulation is a way to stabilize the bioactive compounds from the plant extracts. Previously, encapsulation techniques have been widely studied in modern drugs. For instance, the hydrophobic drugs such as celecoxib, diosmin, exendin-4, 5-fluorouracil and paclitaxel; and hydrophilic drugs such as amoxicillin and insulin. Euphorbiaceae is a family of kingdom Plantae rich in pharmaceutical constituents that have been proved in traditional medicines but getting less attention in terms of encapsulation studies. Euphorbiaceae has a big potential for the application of drug delivery in pharmaceutical industry by improving their stability using microencapsulation or nanoencapsulation. Similar models in the encapsulation of modern drugs can be used in the encapsulation of plant bioactive compounds according to their hydrophilicity or hydrophobicity. This paper also suggested some plant species in Euphorbiaceae that has never been reported on the encapsulation for next exploration.

Keywords: Drug delivery, encapsulation, euphorbiaceae, microparticles, polymers.

INTRODUCTION

Plants have been used in folk medicines for many centuries and it was recorded by the famous ancient medicine civilization of Ayurvedic and chinese. The bioactive compound extracts from plant has been accepted worldwide as a medication therapeutics due to less side effects as compared to modern synthetic drug molecules. The bioactive compounds being extracted from the plants that has been proved on their therapuetic uses. Euphorbiaceae is a large family of flowering plants category with 300 genera and more than 7500 species. Euphorbiaceae family plants are also known as spurge family [1] which derives from the French word due to the use of the Euphorbia latex as purgative [2] . The presence of milky latex specifically characterized Euphorbiaceae from other plant family [1]. For instance, rubber tree (*Hevea brasiliensis*), is known due to the production of latex from the bark cutting has widely been used as rubber in polymer field. Most Euphorbiaceae family are herbs but some are shrubs or trees in tropical region. Some of these plants can be found only in a certain region and some of them often looked as weeds. *Acalypha* is one of the largest genera in Euphorbiaceae family among 300 genera. Most of *Acalypha* species used as medicinal plants [3, 4].

Even though there are a lot of reviews on the encapsulation of synthetic drugs and some famous herb plant bioactive compound extracts, to the best of our knowledge, less study reported on the encapsulation of Euphorbiaceae plants recently as well as no review on this particular subject. This paper will be discussing on the bioactive compound extracts from Euphorbiaceae plant family that have been encapsulated to improve their stability and suggesting other Euphorbiaceae plants that have big potential to be encapsulated for pharmaceutical applications [5].

BIOACTIVE COMPOUNDS (PHYTOCHEMICALS) IN EUPHORBIACEAE PLANTS FOR ENCAPSULATION

The plant chemistry knowledge is a necessary subject to discover for a better understanding on their medicinal potentials. Before going further on the types of microencapsulations, knowing the kinds of bioactive compods are promising to decide the suitable method of encapsulations and the types of polymer that will be compatible. Basically, plant consists of two classes of metabolites; primary metabolites and secondary metabolites. Primary metabolites carry the basic roles of plants for them to survive for example; cell division and growth, respiration, storage and reproduction [6]. It includes the pathway of glycolysis, Kreb or citric acid cycle and photosynthesis. Whereas, secondary metabolites play the roles in carrying the specific properties of the plants. Secondary metabolites involve numerous chemical compounds in the plant cells through the metabolic pathways which derived from the primary metabolites. In other words, primary and secondary metabolites are working together. It is classified according to the chemical structures. Several classes of secondary plant metabolites are; alkaloids, phenolic compounds, saponins, terpenes, lipids and carbohydrates [6].

Alkaloid

One of the large and complex group of cyclic compounds containing N is alkaloids and majority of them are derived from amino acid [7]. Some of the important alkaloids are caffeine, morphine, strychnine, atropine, colchicine, ephedrine, quinine and nicotine. Alkaloids can be found commonly in herbaceous plants. Usually high concentration of alkaloids are found in leaves, bark or roots of the plants. Pure alkaloids usually formed in colorless, odorless crystalline solids and sometimes yellowish liquids [8]. According to Duraiarasan et al. (2011) [9], alkaloids were tested forming white colour.

Alkaloids are widely used in pharmaceutical industry and the effectiveness almost similar with other synthetic drugs. Alkaloids have been reported to reduce the ulceration [10]. Besides, quinine is one of the powerful antimalarial agent. Owing to the quinine is from the natural sources, it possess less toxicity towards body system [8].

Phenolic Compounds

Phenolic compounds also known as polyphenol are the second most abundant group of secondary phytochemicals. Each groups carry their own functions and make up the specific features of the plants. Most of insoluble phenolic compounds can be extracted by methanolic or ethanolic extracts. Phenolic compounds are classified into two main groups; flavonoids and nonflavonoids. The main groups of phenolic compounds are; flavonoids. The most abundant group of phenolic compounds exist in plants are flavonoids which is most bioactive. Whereas the groups of nonflavonoids are phenolic acids, tannins, stilbenes and lignans. The basic structure of flavonoids contain a phenyl benzopyran skeleton (Fig. 1) [11]. Even though most of plants kingdom having phenolic compounds, however, some families possess the specific derivatives thus make up the special features to the family. For instance, capsaicin is the derivatives of capsaicinoids only found in genus *capsicum* (family: solanaceae) [11] whereas *Euporbia hirta* L. contains rutin, quercitin, euphorbin-D which differ from other families [12].

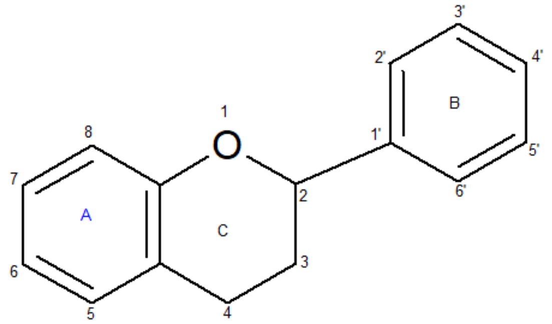

Fig. 1 Phenyl benzopyran skeleton is the basic structure of flavonoids

The most basic structure of flavonoids are Flavones (Fig.1) with the presence of a keto group in C4, double bond between C2 and C3 and another one benzene ring attached to C2. The isomer of flavones which is isoflavones that switch the location of one benzene ring attached to C3 instead of C2 thus making the structural features resemble with estrogens (female sex hormones). Interestingly, this special features can be found in *Acalypha indica* and this plant is commonly known as phytoestrogenic plants [13].

Phenolic compounds were recorded as the most dominant compounds in Euphorbiaceae plants for antioxidant activities [2]. Other than that, phenolic compounds showed good anti-inflammation properties because of the ability to inhibit the cyclooxygenase and lipooxygenase pathway which causing inflammation [14]. The effect of phenolic compounds are similar with the modern drugs such as aspirin and ibuprofen to inhibit the cyclooxygenase activity [15].

Next, kaemferol and quercetin are derivatives of flavonols group. Quercetin has been proved scientifically good for anti-inflammatory properties. Asthma is a chronic respiratory disease due to inflammation in airways. It was induced by the allergens and mediated by Th2 cell-related immune responses. A study was done in *Euphorbia hirta* L. that has possible anti-asthmatic effects of quercetin [16].

Phenolic compounds are preferable to be extracted using the polar solvent of ethyl acetate and methanol, ethanol and hexane [17]. The selection of suitable solvents for extractions are important to maximize the extraction efficiency and reduce loss of other bioactive compounds from the plant matrices. This is due to the chemical nature of each types of bioactive compounds affects the yields. The aqueous mixture of the ethanol, methanol, acetone and ethyl acetate solvents have been discovered by previous study as the most suitable solvents. For instance, ethanol is a good solvent for polyphenol extraction, methanol for the low molecular weight of polyphenol and acetone is good for flavanols extractions. [18, 19].

Terpenoids

Terpenoids also known as isoprenoids are the other bioactive compounds that abundantly found in Euphorbiaceae plants. Triterpenes are the classified under terpenoid family. Triterpenes can be found in cyclic structure. Then from the cyclic triterpenes the structures are being changed forming sterols, steroids and saponins. Saponins have been found in *Acalypha indica* plants and reported by Kalimuthu and his coworkers (2010) [10] by simple saponins detection test through the formation of foams after the extracts being agitated.

Essential oils

Essential oils are the concentrated aromatic oily liquids which containing abundant mixtures of volatile active compounds that can be extracted from certain parts of plants [20]. The method of extractions differed from other bioactive compound extracts due to the properties which is water soluble. The essential oils can be found in many types of plants especially the aromatic plants. Interestingly, the extraction will be done specific in certain plant organs that found abundant of essential oils according to the studies [20]. Until now, the common family plants that has been widely exploited for essential oil extractions are Burseraceae [21], Lamiaceae, and Myrtaceae. In Euphorbiaceae, the essential oil has been extracted from *Euphorbia hirta* L. for asthma treatment. Essential oil benefits most the pharmaceutical industry. Other than that, the food industry, healthcare also benefits the essential oil to improve the appearance of their products as the essential oil not only has antimicrobial properties, but also contributing the good fragrances naturally.

METHODS OF ENCAPSULATIONS

Encapsulation is a process in which the tiny particles of bioactive compounds are being capped by coating or surrounded in a homogenous or heterogeneous environment giving small capsules with vast beneficial properties [22]. Special attention the materials used for encapsulation of plant bioactive compounds are from the utilization of FDA approved synthetic polymers enable the engineering of controlled releasing rate of that bioactive compounds from the polymer matrix depending on the properties of both drug and the polymer [23]. Besides, encapsulations also can improve the solubility of insoluble bioactive compounds and enhanced the targeted drug delivery [24]. Fig. 2 shows the common pathway for the drugs or active compounds administration orally into the drug delivery system. The incorporation with drying process in the microencapsulations enable the liquid microparticles converted into powder form. Spray dry and freeze dry are the types of drying process resulting better coating and more stable for longer storage period.

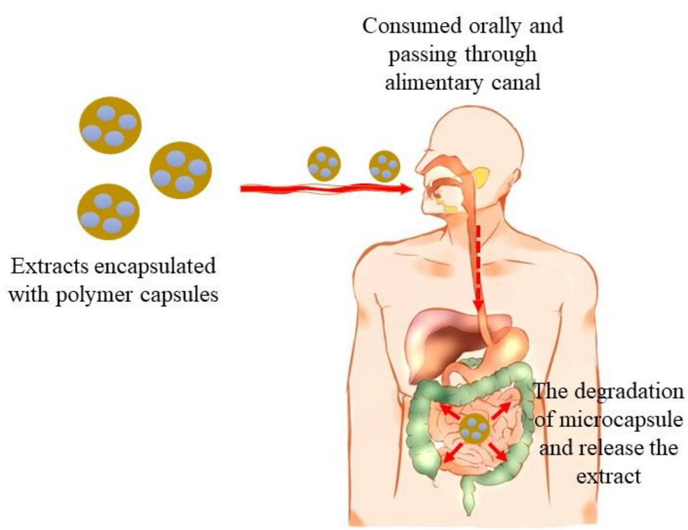

Fig. 2 The design of common route of active compounds administration in drug delivery system.

This technology is very good to apply on the less stable materials such as the volatile phytochemical extracts. Also, the problems faced by polyphenols are lacking of shelf life due to the sensitivity towards light and heat can be solved by encapsulations. In addition, naturally polyphenol tasted bitter and astringent as well as lack of water solubility. So the encapsulation is very promising [25]. Each types of bioactive compounds have their specific kinds of extraction including the selection of solvents depending on the polarity and the steps of extractions must be considered [26, 27]. Thus, the encapsulation techniques are depend on the types of plant extracts so that the bioactive compounds and the encapsulation will be compatible. Table 1 summarized some of the reported encapsulation studies on Euphorbiaceae plants.

Table 1 The Euphorbiaceae plant extracts that has been encapsulated by previous study

Plants	Active compounds	Method of encapsulations	Applications	References
Emblica officinalis	Polyphenols and gallic acid(Water-soluble extracts)	Water-in-oil-water (W/O/W) double emulsion	Drug delivery	[28]
Euphorbia hirta L.	Flavonoid, Phenolic	Extract mixed with 20% maltodextrin with ratio 1:10 and spray drying	Antidiabetic	[29]
Macaranga gigantea	Ethanolic crude extracts- Alkaloids, Flavonoids, tanins, phenolic, and steroids (less water soluble)	Oil-in- water (O/W) Solvent evaporation method	Antitumor, anticancer, antimalaria, antimicrobes, antioxidant	[15]

BLENDING – PHYSICAL MODIFICATIONS

Hydrophobic extracts: Emulsions- solvent evaporation method

Emulsions- solvent evaporation method is the most frequent and facile method used to synthesis the polymer encapsulation. This method consists of two phases which are aqueous and organic phase. This method involves the dissolving of a poorly soluble bioactive plant extracts into the polymer/solvent solution. Then followed by the emulsification of the solutions into an aqueous phase. Then, the solutions will be evaporated and the polymers with the drug are precipitated as the microspheres [30].

Single emulsions often classified as hydrophilic water-oil (W/O) and lipophilic oil-in-water (O/W) and it was illustrated in Fig. 3. One of the most important ingredients is the surfactants are used to form the kind of emulsions. The solubility of the surfactants resulting the types of emulsions formed. For instance, hydrophilic surfactants such as polyvinyl alcohol (PVA) promote the O/W emulsions whereby hydrophobic surfactants promote the W/O emulsions. Surfactants are also important emulsifying agents as it made emulsions more stable [31]. The selection of the types of emulsions are depending on the properties and indications of the bioactive compounds [32]. The method of O/W has been used by Muhaimin et al. (2020) [15] by encapsulating the methanolic extracts of *Macaranga gigantea.*

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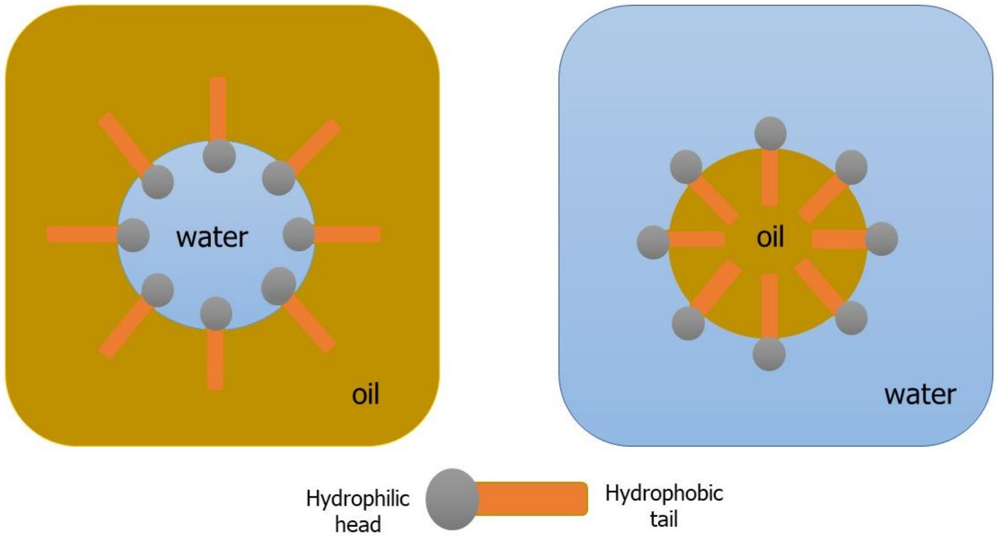

Fig. 3 a) water-oil (W/O) emulsion, b) oil-water (O/W) emulsion

The advantage of this method is the particle size formed can be adjustable by changing the homogenization speed and the amount of stabilizer. Thus, it will affecting the loading capacity, the encapsulation efficiency and the kinetic release of the encapsulated bioactive compounds. Besides, the use of partially hydrolyzed polyvinyl alcohol (PVA) as a surfactant can give the smallest microspheres [33].

Hydrophilic extracts: Double emulsion and evaporation method

Double emulsion is a complex system because of the droplets of first phase is dispersed into the second phase. To improve the emulsion-solvent evaporation method as this method only suitable to be applied on hydrophobic drug, double emulsion method was designed to encapsulate the water-soluble drug.

There are two common types of double emulsion which are; water-oil-water (W/O/W) and oil-water-oil (O/W/O). These methods are similar but different in sequence of mixing and depend on the types of active compounds that are encapsulated. The double emulsion involves two steps (Fig. 4). In the first step of W/O/W double emulsion preparation, the inner aqueous phase (W1) is dispersed in the oil phase containing the lipophilic surfactant. Then followed by the dispersion of the primary emulsion into the outer aqueous phase (W2) containing hydrophilic emulsifier.

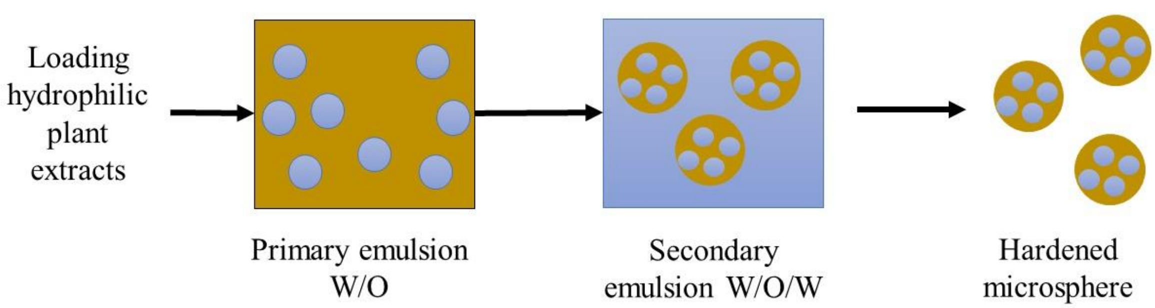

Fig. 4 The double emulsion solvent evaporation method for the microencapsulation of hydrophilic plant extracts

Grafting- chemical modifications

The chemically modified of polymers by grafting has been done successfully in the encapsulation of synthetic drugs and to the best of our knowledge, no study reported on the polymer modification by grafting of two or more types of polymers for encapsulation of euphorbiaceae plants. Hence, we would like to suggest this method as a new exploration in drug delivery study for encapsulation of bioactive extracts especially for Euphorbiaceae plants. Grafting is a chemically modified polymers through the covalent bonding to improve their properties. As compared to blending techniques, the modification through grafting giving more structural stability towards any changes of environment without altering the main skeleton [34]. Besides, grafting also produce a novel hybrid polymers with well-defined structure thus improving the encapsulation system of bioactive compound materials [35].

Recently, chitosan is the most promising natural biopolymer has been use in the encapsulation study for drug delivery due to its special characteristics in terms of biocompatibility, bioavailability as well as FDA approved polymer. Grafting of chitosan with other FDA-approved synthetic polymers such as poly-ε-caprolactone (PCL) [36] and Poly-ethylene glycol (PEG)[37] have been done by series of experiment by Liu and coworkers (2004& 2005) [36, 38] by ring-opening polymerization (ROP). This method is a well established method to copolymerize chitosan as the chitosan structure composed of cyclic monomers of glucosamine and the acrylic acid create the homogenous cleavage of C-C bonds of chitosan saccharide units. Free radicals are produced and initiates the graft copolymerization and towards the end, a new hybrid structure is formed [39]. In some studies, sodium tripolyphosphate (TPP) has been used as a crosslinking agent during the grafting of chitosan with PEG to improve their chemical stabilities and improving the pharmacokinetic property of the encapsulated bioactive materials [40].

CONCLUSION AND FUTURE OUTLOOK

The discovery of Euphorbiaceae plants found a lot of medicinal values as it has been utilized by folks people since ancient time but get less attention among modern research and developments. There are a few studies reported on the encapsulation of Euphorbiaceae plants with biocompatible polymers and more exploration will open up new novelty of this area of research. This paper can be a fundamental study to bring up the potential extracts of Euphorbiaceae plant loaded microparticles for transformation into the pharmaceutical products.

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