EXTRACTION AND MICROENCAPSULATION OF POLYPHENOL-RICH ANTIOXIDANT FROM *CLINACANTHUS NUTANS* FOR CONTROLLED RELEASE FORMULATION

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DEDICATION

In the name of Allah, the Most Gracious, the Most Merciful,

This page is specially dedicated to my beloved mother and father,

Jermiah binti. Haji Ariff

&

Abdul Karim bin Mohd Said

Thanks for all the tremendous love, prayer, believe,
support, patience and all the times both of you
stood by my side and gave me strength
to finish my studies.

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ABSTRACT

Clinacanthus nutans (Burm.f.) Lindau is a herbal medicine traditionally consumed in Malaysia. Since most of herbal active compounds are complex and may cause interferences in human body, a delivery system is needed to control the delivery of the active compounds. Thus, this study aims to develop controlled release formulated *C. nutans* polyphenolic-rich antioxidant extracts. Firstly, standardize *C. nutans* extracts were prepared by extracting the leaves and stem by different extraction methods and type of solvents. The extracts were characterized based on the content of polyphenol (TPC), total flavonoid (TFC), four composition of C-glycoside flavones (vitexin, isovitexin, orientin, isoorientin), total antioxidant capacity (TAC) and other chemical antioxidant compounds using gas chromatography–mass spectrometry. Then, *C. nutans* leaves extracts were encapsulated in carrier agent (κC/CMC) and spray dried to obtain extract in powder form. The feed flow rate, inlet drying temperature and coating agent concentration were studied and the physicochemical properties and release profile for uncoated and coated spray-dried *C. nutans* were characterized. The antioxidant capacity of spray-dried *C. nutans* was then predicted using artificial neural network (ANN) model. From the results, a standardized extraction was obtained from *C. nutans* leaves extract using decoction method with high extraction efficiency of polyphenolic compounds and antioxidant properties with TPC of 44.76 mg gallic acid equivalent (GAE)/g, TFC of 7.39 mg quercetin equivalent (QE)/g, TAC_{DPPH} : 16.29 mg trolox equivalent antioxidant capacity (TEAC)/g; TAC_{FRAP} : 29.58 mg TEAC/g of dried extracts. The *C. nutans* leaves extracts enriched with flavonoid glycosides : isoorientin (811.0 µg/mL) as major compound, followed by isovitexin (204.9 µg/mL), orientin (138.5 µg/mL) and vitexin (135.6 µg/mL). The *C. nutans* extracts was successfully encapsulated in κC/CMC by spray drying process at 700 mL/h of feed flow rate, 130 °C of inlet drying temperature and 0.5 % (w/v) coating agent concentration with high encapsulation yield (25.5 %) and high antioxidant capacities (TPC: 41.9 mg GAE/g, TFC: 11.6 mg QE/g, TAC_{DPPH}: 1.3 mg TEAC/g of spray-dried powders). ANN modeling was able provide satisfactory prediction for antioxidant capacities of spray-dried *C. nutans* with high correlation coefficient (R^2) determination for TPC (R^2: 0.8697), TFC (R^2: 0.6562), vitexin (R^2: 0.9543), isovitexin (R^2: 0.9445), orientin (R^2: 0.9586), isoorientin (R^2: 0.8396), and total antioxidant activity (R^2 = 0.8599). The spray-dried encapsulated *C. nutans* had smooth surface and spherical shape with small particle size range between 1.72 to 3.35 µm and good stability with surface charge of -42.6 and polydispersity index (PDI) of 0.45. The uncoated spray-dried *C. nutans* (control) exhibited wrinkle surface and irregular morphology with small particle size of 1.24 µm but poor stability with zeta potential value of -10.2 and PDI value of 0.86 which indicate that coagulation and flocculation will occur. The antioxidant release studies of coated spray-dried *C. nutans* in simulated gastric and intestinal fluids showed burst release of antioxidants in first 5 to 15 min and controlled release up to 240 min. In conclusion, the spray-dried *C. nutans* using κC/NaCMC microspheres is highly suitable for the formulation of herbal product.

ABSTRAK

Clinacanthus nutans (Burm.f.) Lindau adalah ubatan herba tradisional yang digunakan di Malaysia. Memandangkan kebanyakan sebatian aktif herba adalah kompleks dan boleh menyebabkan gangguan di dalam badan manusia, satu sistem penghantaran diperlukan bagi mengawal penghantaran sebatian-sebatian aktif. Jadi, kajian ini adalah bertujuan untuk membangunkan formulasi pengawalan penghantaran polifenolik yang kaya antioksida daripada ekstrak *C. nutans*. Pertama sekali, ekstrak *C. nutans* piawai disediakan dengan mengesktrak daun dan batang dengan pelbagai kaedah pengekstrakan dan jenis pelarut. Ekstrak-ekstrak dicirikan berdasarkan kandungan folifenol (TPC), jumlah kandungan flavonoid (TFC), empat komposisi C-glikosid flavon (viteksin, isoviteksin, orientin, isoorientin), kandungan kapasiti antioksida (TAC) dan sebatian antioksida kimia yang lain menggunakan kromatografi gas-spektrometri jisim. Kemudian, ekstrak daun *C. nutans* disalut dengan agen pembawa (κC/CMC) dan disembur kering untuk menghasilkan serbuk ekstrak. Kadar aliran suapan, suhu pengeringan masukan dan kepekatan agen salutan telah dikaji dan sifat fizikokimia serta profil pelepasan bagi semburan kering *C. nutans* yang tidak bersalut dan bersalut telah dicirikan. Kapasiti antioksida bagi semburan kering *C. nutans* telah diramal menggunakan model rangkaian neural artifisial (ANN). Daripada keputusan, satu pengekstrakan piawai telah diperoleh dari ekstrak daun *C. nutans* menggunakan kaedah pendidihan dengan kecekapan pengekstrakan kandungan folifenol dan antioksida yang tinggi iaitu TPC : 44.76 mg asid galik setara (GAE)/g, TFC : 7.39 mg kuersetin setara (QE)/g, TAC_{DPPH} : 16.29 mg keupayaan antipengoksida troloks setara (TEAC)/g; TAC_{FRAP} : 29.58 mg TEAC/g ekstrak kering. Ekstrak daun *C. nutans* kaya dengan flavonoid glikosid : isoorientin (811.0 µg/mL) sebagai sebatian utama diikuti oleh isoviteksin (204.9 µg/mL), orientin (138.5 µg/mL) and viteksin (135.6 µg/mL). Ekstrak *C. nutans* berjaya disalut dengan κC/CMC melalui proses semburan kering pada kadar alir suapan 700 mL/jam, suhu pengeringan salur masuk 130 °C dan kepekatan agen salutan adalah 0.5% (w/v) dengan hasil salutan yang tinggi (25.5 %) dan kapasiti antioksida yang tinggi (TPC : 41.9 mg GAE/g, TFC : 11.6 mg QE/g, TAC_{DPPH} : 1.3 mg TEAC/g serbuk semburan kering). Model ANN memberikan ramalan yang memuaskan bagi kapasiti antioksida semburan kering *C. nutans* dengan korelasi pekali (R^2) yang tinggi untuk TPC (R^2: 0.8697), TFC (R^2: 0.6562), viteksin (R^2: 0.9543), isoviteksin (R^2: 0.9445), orientin (R^2: 0.9586), isoorientin (R^2: 0.8396), dan jumlah aktiviti antioksida (R^2: 0.8599). Semburan kering *C. nutans* yang bersalut mempunyai permukaan licin dan berbentuk bulat dengan saiz zarah yang kecil antara 1.72 hingga 3.35 μm dan kestabilan yang baik dengan cas permukaan iaitu -42.6 dan indeks poliserakan (PDI) iaitu 0.45. Semburan kering *C. nutans* yang tidak bersalut (kawalan) menunjukkan permukaan berkedut dan tidak sekata dengan saiz zarah yang kecil iaitu 1.24 μm tetapi kestabilan yang rendah dengan nilai potensi zeta iaitu -10.2 dan nilai PDI 0.86 yang mana menunjukkan penggumpalan dan pengendapan akan berlaku. Kajian pelepasan antioksida bagi semburan kering yang bersalut *C. nutans* di dalam simulasi cecair perut dan usus menunjukkan pelepasan antioksida secara mendadak 5 ke 15 min pertama dan diikuti dengan pelepasan secara terkawal sehingga 240 min. Kesimpulannya, semburan kering *C. nutans* menggunakan mikrosfera κC/NaCMC sangat sesuai untuk formulasi produk berasaskan herba.

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LIST OF ABBREVIATIONS

ROS	-	Reactive Oxygen Species
RNS	-	Reactive Nitrogen Species
RSS	-	Reactive Sulfur Species
FDA	-	Federal Food, Drug and Cosmetic Act
TCM	-	Traditional and Complementary Medicines
SFE	-	Supercritical Fluid Extraction
PSE	-	Pressurized Solvent Extraction
EAE	-	Enzyme-Assisted Extraction
P-MAE	-	Pressurized Microwave-Assisted Extraction
MAE	-	Microwave-Assisted Extraction
DE	-	Decoction Method
ME	-	Maceration Method
SE	-	Soxhlet Method
UAE	-	Ultrasonic-Assisted Extraction
ROS	-	Reactive Oxygen Species
FFA	-	Free Fatty Acids
MAG	-	Monoacylglycerols
NMR	-	Nuclear Magnetic Resonance
UPLC-MS/MS	-	Ultra Performance Liquid Chromatography - Tandem Mass Spectrometer
HPTLC	-	High-performance thin-layer chromatography
HSQC	-	Heteronuclear single quantum coherence spectroscopy
DNA	-	Deoxyribonucleic acid
LD_{50}	-	Median Lethal Dose
IC_{50}	-	Half Maximal Inhibitory Concentration
MTT	-	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromidefor
MIC	-	Minimum Inhibitory Concentration
MBC	-	Minimum Bactericidal Concentration
ET	-	Electron Transfer

HAT	-	Hydrogen Atom Transfer
FC	-	Folin-Ciocalteu
DW	-	Dried Weight
TPC	-	Total Phenolics Content
TFC	-	Total Flavonoids Content
AA	-	Antioxidant Activity
ABTS	-	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
FRAP	-	Ferric Reducing Antioxidant Power
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
AA_{FRAP}		Antioxidant Activity measured by FRAP
AA_{DPPH}		Antioxidant Activity measured by DPPH
GAE	-	Gallic Acid Equivalent
QE	-	Quercetin Equivalent
TEAC	-	Trolox Equivalent Antioxidant Capacity
OFAT	-	One-Factor-at-A-Time
ANN	-	Artificial Neural Networks
MBP	-	Multiple Back Propagation
SDP	-	Spray-Dried Powders
κC	-	Kappa-Carrageenan
NaCMC	-	Sodium Carboxymethyl Cellulose
FESEM	-	Fourier Electron Scanning Electron Microscopy
FTIR	-	Fourier transform infrared spectroscopy
HPLC	-	High-performance liquid chromatography
GC-MS	-	Gas chromatography–mass spectrometry
NaOH	-	Sodium Hydroxide
HCl	-	Hydrochloric acid
rpm	-	Rotation Per Minute

LIST OF SYMBOLS

g	-	Gram
mg	-	Miligram
L	-	Liter
M	-	Molar
g	-	Gram
%	-	Percentage
°C	-	Degree Celcius
α	-	alpha
β	-	beta
κ	-	kappa
µ	-	micro
pH	-	potential of Hydrogen
≤	-	Less-than or equal to
<	-	Less-than
≥	-	More-than or equal to
>	-	More-than
mg	-	Miligram
g	-	Gram
L	-	Liter
M	-	Molar
v	-	Volume
v/v	-	Volume per volume
w	-	Weight
w/v	-	Weight per volume
λ	-	wavelength
R_t	-	Retention Time
R^2	-	Correlation Coefficient
kHz	-	Kilohertz
GHz	-	Gigahertz

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

In modern civilization, some people tend to have inactive and unhealthy lifestyle filled with stressful and hectic schedules. These may lead to the generation of free radicals internally in the body system but also through external sources like environmental pollutions, toxic metals, cigarette smoke, pesticides and others, which is harmful to the body system. Antioxidants are substances which at low concentration significantly inhibit or quench free radical reactions and delay or inhibit cellular damage from the chronic and degenerative diseases such as Alzheimer's disease, cancer, and heart disease (Rajendran *et al*., 2014; Nimse and Pal, 2015). Antioxidants of plant origin with free radical scavenging properties could have great importance as recovery agents in several diseases caused by environmental pollution (Carocho and Ferreira, 2013).

Medicinal plants have attracted global attention for their hidden antioxidant potential and one of the most popular herbs in Malaysia is *Clinacanthus nutans* known as Sabah snake grass (Zulkipli *et al*., 2017). *Clinacanthus nutans* (Burm.f.) Lindau (*C. nutans*), a plant of Acanthaceae is native to Southeast Asia regions of Malaysia, Indonesia, Thailand and China. The leaves have been traditionally used as folk remedies for many diseases, including the treatment of insect bites, herpes infection, allergic responses, diabetes and cancer. It has been reported to be used as an aid in inflammation problem, immune response activity, antidiabetic, anticancer, antimicrobial, and antioxidant activities. It is well established that *C. nutans* is a good source of antioxidants, polyphenols, phytosterols, triterpenoids, vitamin and other bioactive compounds (Sakdarat *et al*., 2009). Teshima *et al*. (1998) have reported the presence of C-glycosyl flavones such as vitexin, isovitexin, shaftoside, isomollupentinin in *C. nutans*. The rich sources of natural flavonoid-antioxidant compounds in *C. nutans* make it valuable to be used as a food supplement as well as health and cosmetic product.

During the development of herbal medicinal products, extraction condition plays crucial role in order to obtain a product with optimum level of active substances. Several decisions need to be considered to determine the set of conditions, which will result in a product with an acceptable combination of physical and chemical properties. The definition of the production course involves the evaluation of the effects of several parameters on the desired responses by studying its effects on the process and their possible interactions. This is a problem involving the simultaneous optimization of several response variables (the desirable combination of properties), which depend of a number of independent variables or sets of conditions. Different kind of methods and solvents had been used to get extracted herbs. The most commonly employed mean of consuming medicinal herbs is preparing a traditional remedy by making an aqueous infusion or decoction from the valuable parts of plants such as flowers, leafs and roots (Belščak-Cvitanović *et al*., 2011). The herb compounds need to be extracted carefully and in virgin state, thus needed a suitable extraction conditions in order to get the maximum yield with desired compound of herbs extract (Azmir *et al*., 2013).

Polyphenols acts as free-radical scavenging and inhibition of oxidizing processes in the body. Polyphenol compounds in plant are important because they provide a natural antioxidant capacity (Santiago-Adame *et al*., 2015). Since most polyphenols are hydrophilic compounds which require an extraction process in order to be exhausted from the source material, their direct use in food matrix is limited. This problem can be solved by applying the microencapsulation technology, which provides the required technique for conversion of the liquid extract to an effective functional ingredient. The intake of natural bioactive compounds, especially polyphenols through herb is of great interest, but difficulties associated with the susceptibility of those compounds to adverse external effects, or detrimental food processing conditions and their chemical instability have provided many efforts to improve oral bioavailability (Belščak-Cvitanović *et al*., 2011).

Microencapsulation processes such as spray drying have proven to be an effective technology for protecting polyphenol compounds. Spray-drying is an economical, flexible, well-established and widely used technique produces particles with good quality for transforming liquid foods or suspensions into a powder in a one-step process (Fang and Bhandari, 2010). The application of microencapsulated polyphenol compounds as functional ingredients in various food and beverage applications exhibits a significant potential, since it could enable the enrichment of various food products with natural antioxidants (Belščak-Cvitanović *et al*., 2011). Several encapsulation studies of polyphenolic antioxidants has been reported using spray drying as the encapsulation technique such as the encapsulation of polyphenolic compounds of laurel infusions (*Litsea glaucescens*) (Medina-Tores *et al*., 2016), ginger (*Zingiber officinale*) (Simon-Brown *et al*., 2016), cinnamon (*Cinnamomum zeylanicum*) (Santiago-Adame *et al*., 2015), yerba mate (*Illex paraguariensis*) extract (Nunes *et al*., 2015; Deladino *et al*., 2008), St. John's wort (*Hypericum perforatum*) extract (Kalogeropoulos *et al*., 2010), cactus pear (*Opuntia ficus indica*) (Saénz *et al*., 2009), *Crataegus monogyna* Jacq. (Bucco *et al*., 2009) and a traditional Chinese medicinal plant *Radix Salvia millthiorhiza* (Su *et al*., 2008).

Among polyanionic polymers used to encapsulate the desired compounds, combination use of kappa-carragenaan and carboxymethyl cellulose of sodium salts have received much attention lately in drug delivery system for their excellent controlled release of the drugs (Muhamad *et al*., 2011; Hezaveh *et al*., 2012; Hezaveh and Muhamad, 2012a; 2012b; Hezaveh and Muhamad, 2013a; 2013b; Selvakumaran and Muhamad, 2014; 2015; Selvakumaran *et al*., 2016). Carrageenan also has wide applications in food and pharmaceutical industry such as thickener, emulsifier, binder, stabilizer and also tablet disintegrant, for the production of controlled release solid dosage (Li *et al*., 2014). According to literature survey, Suhaimi *et al*. (2013) have performed the encapsulation of aqueous *C. nutans* extracts in maltodextrin by spray drying. However, they only focused on the physico-chemical properties such as moisture content, water activity, protein, bulk density, oil content, ash, crude fibre and colour (L^*, a^* and b^*) of spray-dried *C. nutans*, and did not further investigate the retention of the polyphenolic antioxidant compounds after spray-dried process. Meanwhile, Mustapa *et al*. (2016), impregnated phytol (major compounds) from *C. nutans* extracts into silica and alginate aerogels and further studied the release of this compound from the matrix. However, so far, there is no report on the encapsulation of polyphenolic compounds from *C. nutans* extracts and the release profile of them.

Therefore, this study was to develop an oral administration formulation for *C. nutans* by finding the convenient and best method for extracting the major antioxidant compounds and further encapsulated in kappa carrageenan-carboxymethyl cellulose microspheres through spray drying process. The antioxidant potential and physicochemical characterization of encapsulated herbal polyphenolic *C. nutans* extracts has been investigated. The release profile of antioxidant for the uncoated and coated spray-dried microspheres were determined.

1.2 Statement of Problem

In recent years, increasing numbers of people have been choosing herbal medicines or products to improve their health conditions, either alone or in combination with others. Herbs are staging a comeback and herbal 'renaissance' occurs all over the world. According to the World Health Organization, 75% of the world's populations are using herbs for basic healthcare needs. Since the dawn of mankind, in fact, the use of herbs/plants has offered an effective medicine for the treatment of illnesses (Pan *et al*., 2014).

Clinacanthus nutans (*C. nutans*) Lindau has been used as vital herbal medicines in tropical Asia and this plant attracts much attention of many researchers for its medicinal potencies such as antioxidant, anti-viral, antimicrobial, anti-inflammatory, immune response activity, anti-venom, anti-dengue and anti-tumorigenic activities (Zulkipli *et al*., 2017; Alam *et al*., 2016). In addition, Thailand Ministry of Public Health has considered this plant as one of main remedies for the treatment of skin inflammations and lesion caused by virus (Wanikiat *et al*., 2008). Behind those pharmacological properties, there are varieties of chemical compounds reported such as betulin (Lin *et al*., 1983), C-glycosyl flavones (vitexin, isovitexin, shaftoside, isomollupentin-7-O-β-glucopyranoside, orientin, isooreintin) (Teshima *et al*., 1998), sulfur-containing glycosides (Teshima *et al*., 1998), two glycoglycerolipids, a mixture of nine cerebrosides and a monoacylmonogalatosylglycerol (Tuntiwachwuttikul *et al*., 2004), stigmasterol, lupeol, β-sitosterol (Dampawan *et al*., 1977; Cheong *et al*., 2013), and others.

Herbal *C. nutans* bioactives compounds are important category of nutraceuticals consist of diversities of bioactive phenolic compounds or antioxidants that can scavenge free radicals which have a vital role in the improvement of different diseases. Herbal *C. nutans* are normally prepared and consumed based on prescriptions of specific applications. Traditionally, these herbal was prepared by maceration (soaking method), infusion or decoction in water or alcohol that normally in liquid form, which can easily contaminate with other pathogens. In addition, direct and continuous consumption of herbal *C. nutans* compounds can cause interferences or unwanted side effects due to its different reactivity towards human body (Chan *et al*., 2010). This fact was also confirmed by several researchers that found DNA damage, increase phatelet counts, lower level of creatinine, serum alkaline phosphatase and significant body weight loss in male rats as compared to female rats after oral administration of *C. nutans* crude extracts for a certain period of time (Chavalittumrong *et al*., 1995; Kunsorn *et al*., 2016; Farsi *et al*., 2016).

To overcome the problems related with the direct use of bioactives in their free form in *C. nutans* crude extracts, the encapsulation by spray drying technique, through the development of micro-sized particle systems, will ensure protection of the bioactive compounds and, additionally, functional properties to the final product. From the standpoint of herbal products, microencapsulation could achieve a number of desirable effects that includes controlled-delivery, extending shelf-life, separating incompatible compounds and improving final product qualities (Chan *et al*., 2010; Kosaraju *et al*., 2006; Deladino *et al*., 2008). For example, controlled-delivery could enhance bioavailability of an active compound by customising the release mechanism or rate in gastro-intestinal tract. In fact, a delivery system may be mandatory if direct consumption of a certain herbal active compound may cause interferences with the human body. In addition, encapsulation may promote better product stability by isolating active compounds from the detrimental effects of oxygen, moisture or incompatible compounds. Therefore, encapsulation could be a useful technological tool for the commercial sector to develop value-added products or to create product differentiation from competitors (Chan *et al*., 2010).

Previously, several studies have been carried out by incorporating the *C. nutans* extract in different formulation for certain applications. Sulaiman *et al.* (2016; 2017) have been developed a nanoemulsion system containing extract of *C. nutans* leaves for transdermal delivery system. Whereas, Mustapha *et al.* (2016) and Suhaimi *et al.* (2013) have carried out studies related to formulation of *C. nutans* extract for nutraceutical applications. Suhaimi *et al*. (2013) used the spray drying method to produce powder form of *C. nutans* leaves extract using maltodextrin (10-12 DE) as a coating agent and evaluated the physico-chemical properties such as moisture content, water activity, protein, bulk density, oil content, ash, crude fibre and colour (L*, a* and b*). However, the availability of compounds after spray-drying process and it functionality for oral administration had not been further investigated. Meanwhile, Mustapha *et al.* (2016) have impregnated the *C. nutans* leaves extract in silica and alginate aerogels to be used as a drug delivery system for major lipophilic phytol compounds found in *C. nutans* extracts. This drawback emphasized the need to encapsulate phenolic compounds from *C. nutans* crude extracts by spray drying method using previously optimized coating agents (kappa carrageenan and carboxymethyl cellulose) (Muhamad *et al*., 2011) and the controlled release of the spray-dried microspheres in the simulated gastrointestinal fluids are determined.

1.3 Objectives of Study

The main objective of this research was to develop nutraceutical formulation from *C. nutans* crude extracts for antioxidant controlled release. The specific objectives were as follows:

1) To evaluate performance of extraction process to extract major compounds and polyphenols-rich antioxidants from *C. nutans*

2) To determine microencapsulation conditions and the antioxidant capacity of flavonoid *C. nutans* microspheres produced at the optimal conditions

3) To characterize the physicochemical properties of the formulation

4) To construct the release profile and determine the kinetics release mechanism of *C. nutans* spray-dried microspheres.

1.4 Scope of Study

In order to develop a formulation of nutraceuticals from *C. nutans*, the scope will follow the objectives. The extraction efficiency of different solvent, extraction method and plant part were elucidated based on extractive yield and antioxidative compounds analysis. The effects of extraction method (hot extraction – decoction, soxhlet; and cold extraction – maceration, ultrasonic), solvent (water, methanol, ethanol) and plant part (leaf and stem) on the extractive yields and antioxidative compounds were examined. The preliminary study of phytochemical compounds was performed in order to determine the vital compounds in *C. nutans* extracts. Then, the antioxidative compounds were evaluated based on total phenolic, flavonoids and antioxidant activity. The antioxidant activity was determined based on two assays: DPPH free radical scavenging activity and reducing power (FRAP) methods to investigate the effectiveness of antioxidants in *C. nutans* towards different methods that specific to their mechanism of actions. Then, the phenolic and flavonoids contents were correlated to the antioxidant activity to obtain the relationship between these values. After that, the polar flavonoid glycosides compounds such as vitexin, isovitexin, orientin and isoorientin were analyzed using HPLC analysis to identify and quantify the exact amount in the *C. nutans* extracts. Further, the GC-MS analysis was performed to screen the other chemical compounds that possibly antioxidative compounds. Selection of the best extraction methods, solvents and plant part was justified based on high yield and high antioxidative compounds.

The next scope is to formulate the *C. nutans* extracts in carrier agent through spray drying process. The formulation (coating agent concentration) and spray drying conditions (feed flow rate, inlet drying temperature) were examined and optimized using one-factor-at-a-time (OFAT). Different coating agent concentration, kC/NaCMC (0.1 – 1.0 % w/v), feed flow rate (500 – 700 ml/h) and inlet drying temperature (110 °C, 130 °C and 150°C) were studied to obtain a good preservation of antioxidative compounds. The retention of phenolic, flavonoid and four marker compounds such as vitexin, isovitexin, orientin and isoorientin were determined and evaluated for the overall antioxidant activity. The uncoated spray-dried and coated spary-dried were compared. The experimental data then fitted in the artificial neural network (ANN) modeling to predict the antioxidant activity of spray-dried *C. nutans*.

This model is used based on reliable, low cost and fast tool and open the way for predicting the overall parameters contributes to overall antioxidant capacities of *C. nutans*.

The characterization of uncoated and coated spray-dried *C. nutans* was further evaluated. The surface morphology of powder produced through spray drying process was examined using SEM analysis. The particle size distribution, polydispersity index and zeta potential of spray-dried powder also evaluated in order to gain insight the stability of the formulation. The chemical structure and interaction between *C. nutans* extracts, coating agent and coated spray-dried *C. nutans* were assessed using FTIR. The colour of the spray-dried product were then determined in order to accomplish the requirement of product acceptance to be marketed.

Lastly, the coated spray-dried *C. nutans* were evaluated for their release profile of overall antioxidant contents. The medium of release fluids was prepared by mimic of the gastrointestinal fluids. The sample was dispersed in simulated gastric fluids (SGF, pH 1.2) and simulated intestinal fluids (SIF, pH 7.4) to investigate the release of antioxidant compounds in different coating agent concentration. Then, the release kinetics and mechanism of coated spray dried *C. nutans* were evaluated based on the fitting experimental release data.

1.5 Significance of Study

The search for safe and effective naturally occurring antioxidants is always focused on plants, especially natural herbal polyphenols which an integral part of the human diet, usually consumed as tea or herbal infusion prepared through aqueous extraction. Antioxidants are highly effective in synergism because of the bioactive components present and their interaction. Furthermore, different antioxidants scavenge different free radicals and responsible for recovering different parts of body cell (Krishnaiah *et al.*, 2012). The selection of the best extraction methods, solvents and plant materials could be significant for optimum antioxidant herbal *C. nutans* formulations. In order to evaluate the stability of the phytochemical compounds towards heats, two extraction methods have been employed which are hot extraction and cold extraction. It is important to know the right extraction methods for optimum extracted compounds. The choice of solvents such as water, ethanol and methanol were used to extract polyphenolic-antioxidant compounds. In literature, many studies have reported on phytochemicals compounds of leaf part of *C. nutans* and only few studies reported on stem part. Therefore, it is economical to use both leaves and stem of *C. nutans* to evaluate the phytochemical components.

It has been recognized that single active compounds may not always be sufficient to provide optimum effects. Therefore, the *C. nutans* crude extracts that consist of multi-component antioxidants could affect the health of an organism through complex and multi targeted interactions. Variations in the levels of phytochemicals could affect the quality control of herbal formulations. In addition, direct consumption of herbal active compound may cause interferences and different side effect towards the human body. Thus, one way to preserve and promote controlled release of the multiple health-promoting properties of antioxidant polyphenols is through encapsulation processes. Microencapsulation using spray drying method is a well-established and widely used technique for transforming liquid foods or suspensions into powder in a one-step process. The microencapsulation technique of spray-drying is an effective way to protect polyphenolic compounds against deterioration and volatile losses through the protective mechanism consists of the formation of a membrane wall that encloses droplets or particles of the encapsulated material. In addition, it is very easy to industrialise and allows for continuous production (Su *et al*., 2008). Hence, this study was performed to ensure that the active compounds are maintained in a bioactive form within the gastrointestinal tract, and promoting a controlled release formulation. The physicochemical characterization and in vitro release studies was performed to investigate the stability of the uncoated and coated spray-dried *C. nutans*. Thus, the developed coated spray-dried *C. nutans* rich with polyphenolic-antioxidant compounds potentially to be used for nutraceutical applications.

1.6 Thesis Outline

This thesis is divided into five chapters and the content of each chapters are described as follows:

Chapter 1 introduces the background of study, statement of problem, objectives, scope and significance of study as well as the framework of the thesis. In this chapter, the problem which led to the research being conducted, the aim of the study and the importance, novelty and hypothesis of this research were clearly stated.

Chapter 2 covers the concept and definition of free radicals, antioxidants and polyphenolic compounds. The previous studies on *Clinacanthus nutans* has been overview for its botanical, traditional uses, pharmacological and phytochemical properties. Various methods for extraction, microencapsulation by spray drying method, release of drugs and phytochemical/bioactive compounds identification and quantification have been reviewed. The mathematical modeling of optimization (one-factor-at-a-time, OFAT; artificial neural network, ANN) and kinetic models (Zero-order, First-order, Hixson–Crowell, Higuchi, and Korsmeyer–Peppas) for bioactive compound release were reviewed. Lastly, this chapter summarized and justified the work that has been studied.

Chapter 3 shows the research methodology for microencapsulation of polyphenolic-antioxidant microspheres from *C. nutans* using spray drying process. The experimental design starting from the extraction, identification and quantification of vital compounds, microencapsulation, ANN modeling, physicochemical characterization of spray-dried powder, release profile, kinetic model and release mechanism of the coated spray-dried *C. nutans*.

Chapter 4 elucidates the results and discussion on three major section in developing of polyphenolic-antioxidant microspheres from *C. nutans*. The first section discussed the influence of extraction methods, solvents and plant parts on extraction yield and antioxidant activity of the extracted *C. nutans*. The evaluation of four flavonoid glycosides as marker compounds and other chemical compounds found in *C. nutans* were further explained. The selection of the best extraction methods, solvents and plant part was discussed. Then, the second section discussed the properties of *C. nutans* after spray-dried in the different coating agent concentration and spray drying conditions (feed flow rate and inlet air drying temperature). The chemical properties such as retention of antioxidant compounds (phenolic, flavonoids, four marker compounds and chemical interaction) and physical properties (particle size, morphology, colour, zeta potential) of spray-dried *C. nutans* were explained. Moreover, the ANN modeling was satisfactory in predicting the antioxidant capacities of spray-dried *C. nutans*. The release, kinetics and mechanism of release compounds from different coating concentration were discussed and well-explained.

Chapter 5 concludes all the findings of this research and propose several recommendations for future research.

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