UNIVERSITI PUTRA MALAYSIA

SOLUTION-ENHANCED DISPERSION BY SUPERCRITICAL CARBON DIOXIDE IN PRODUCTION OF Andrographis paniculata (Burm.f.) Wall. Ex Nees POWDER

LEE SIN YEE

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By

LEE SIN YEE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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Chairman : Associate Professor Chong Gun Hean, PhD
Faculty : Food Science and Technology

Andrographolide with poor aqueous solubility and poor dissolution rate is predisposed to low oral bioavailability. To overcome these constraints, strategies (reducing crystallinity and increasing surface area) were employed through Solution-Enhanced Dispersion by Supercritical Carbon Dioxide (SEDS). SEDS precipitation of *Andrographis paniculata* (Burm.f.) Wall. ex Nees extract from CO_2-Acetone and CO_2-Acetone:Ethanol (v/v) 1:1 systems at different pressure (100, 150 bar) and temperature (40, 50 ˚C) combination as well as aqueous solubility of andrographolide precipitated were first studied. Modification of its aqueous solubility was then conducted by manipulating precipitation using CO_2-Acetone:Ethanol (v/v) of different proportions at selected pressure-temperature combination. Results showed that the low crystalline *A. paniculata* extract powder precipitated from CO_2-Acetone system at 150 bar, 40 ˚C had the highest aqueous solubility of andrographolide (0.06 mg/mL), a two-fold increment than extract. However, absorption of andrographolide could still be poor for its low dissolution rate in Simulated Intestinal Fluid (SIF), pH 7.4 (0.06 mg/mL release in 90 min). Therefore, SEDS co-precipitation of *A. paniculata* with polymers were conducted using the best SEDS precipitation parameters (150 bar, 40 ˚C, CO_2-Acetone system). SEDS co-precipitated *A. paniculata* with Pluronic F127 or Eudragit EPO exhibited poorer andrographolide dissolution in SIF (< 0.03 mg/mL release in 90 min). SEDS co-precipitated *A. paniculata* with Eudragit L100-55 in Eudragit L100-55:*A. paniculata* mass ratio (2:25) showed improved dissolution rate of andrographolide in SIF (0.06 mg/mL release in 45 min) and mass ratio increment to 6:25 resulted in higher andrographolide release and dissolution rate (0.09 mg/mL release in 30 min). Only 20-30% of andrographolide from SEDS co-precipitates (6:25) was degraded after two-month storage whereas 30-60% of andrographolide was degraded after addition into beverages in a day. Since acetone content in SEDS co-precipitates (6:25) was < 0.1 ppm, its increased brine shrimp cytotoxicity (LC_{50} = 46.46 µg/mL) could be attributed to higher aqueous solubility and dissolution rate of andrographolide.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

***SOLUTION-ENHANCED DISPERSION BY SUPERCRITICAL CARBON DIOXIDE* DALAM PENGHASILAN SERBUK *Andrographis paniculata* (Burm.f.) Wall. ex Nees**

Oleh

LEE SIN YEE

November 2018

Pengerusi : Profesor Madya Chong Gun Hean, PhD
Fakulti : Sains dan Teknologi Makanan

Sifat ketidaklarutan dalam air dan kadar pembubaran *andrographolide* yang lemah mengakibatkan kecenderungannya kepada kadar kemasukan yang rendah. Strategi-strategi seperti pengurangan kristalografi dan peningkatan kawasan permukaan sedia ada untuk pembubaran *andrographolide* telah dilaksanakan melalui *Solution-Enhanced Dispersion by Supercritical Carbon Dioxide (SEDS)*. Kajian dimulai dengan mengidentifikasikan trend presipitasi *SEDS* ekstrak *Andrographis paniculata* (Burm.f.) Wall. ex Nees daripada sistem karbon dioksida (CO_2)-Aseton dan sistem CO_2-Aseton:Etanol (v/v) 1:1 dalam kombinasi tekanan (100, 150 bar) dan suhu (40, 50 ˚C) berbeza. Perubahan kelarutan dalam air *andrographolide* selepas presipitasi turut dikajikan. Modifikasi kelarutannya dalam air kemudian dilaksanakan melalui perubahan presipitasi dengan penggunan sistem CO_2-Aseton:Etanol dalam proporsi berlainan (v/v) pada kombinasi tekanan dan suhu ditentukan. Didapati bahawa serbuk ekstrak *A. paniculata* dipresipitasikan daripada sistem CO_2-Aseton pada 150 bar, 40 ˚C mengalami pengkristalan rendah dan mempunyai kelarutan dalam air *andrographolide* yang tertinggi (0.06 mg/mL), peningkatan berganda berbanding ekstrak. Namun, penyerapan *andrographolide* akan disekat jika kadar pembubarannya masih rendah dalam persekitaran *Simulated Intestinal Fluid (SIF)*, pH 7.4 (0.06 mg/mL pembubaran dalam 90 min). Oleh itu, kopresipitasi *SEDS* ekstrak dengan polimer telah dilaksanakan berdasarkan parameter presipitasi *SEDS* terbaik (150 bar, 40 ˚C, sistem CO_2-Aseton). Kopresipitasi *SEDS* ekstrak dengan Pluronic F127 mahupun Eudragit EPO melemahkan pembubaran *andrographolide* dalam persekitran *SIF* (< 0.03 mg/mL pembubaran dalam 90 min). Kopresipitasi *SEDS* dengan nisbah jisim Eudragit L100-55 dan ekstrak (2:25) meningkatkan kadar pembubaran *andrographolide* dalam persekitaran *SIF* (0.06 mg/mL pembubaran dalam 45 min). Peningkatan nisbah jisim hingga 6:25 turut meningkatkan pembubaran dan kadar pembubaran *andrographolide* dalam persekitaran *SIF* (0.09 mg/mL pembubaran dalam 30 min). Hanya 20-30% *andrographolide* daripada serbuk kopresipitasi *SEDS* (6:25) mengalami degradasi selepas dua bulan penyimpanan malah 30-60% *andrographolide* mengalami degradasi selepas sehari dimasukkan dalam minuman. Oleh sebab kandungan sisa aseton serbuk kopresipitasi *SEDS* yang rendah (<

0.1 ppm), peningkatan aktiviti sitotoksiknya terhadap udang air garam (LC_{50} = 46.46 µg/mL) berkemungkinan disebabkan oleh peningkatan kelarutan dan kadar pembubaran *andrographolide*.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Chong Gun Hean, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Luqman Chuah Abdullah, PhD
Professor
Faculty of Engineering
Universiti Putra Malaysia
(Member)

Russly Abdul Rahman, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Member)

Faridah Abas, PhD
Associate Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Member)

_____
ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature: _____
Name of Chairman of Supervisory Committee: Associate Professor Dr. Chong Gun Hean

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Luqman Chuah Abdullah

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Russly Abdul Rahman

Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Faridah Abas

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LIST OF ABBREVIATIONS

AF	Amount of Andrographolide in SEDS Feed
AG	Andrographolide
AR	Andrographolide Recovery
ARISE	Atomized Rapid Injection for Solvent Extraction
AS	Amount of Andrographolide in SEDS Precipitated *A. paniculata* powder
ASES	Aerosol Solvent Extraction System
AUC	Area under the Curve (Plasma Concentration)
BCS	Biopharmaceutics Classification System
C_{max}	Maximum Concentration
$C_{max, pH\ 1.2}$	Maximum Concentration in Simulated Gastric Fluid, pH 1.2
$C_{max, pH\ 7.4}$	Maximum Concentration in Simulated Intestinal Fluid, pH 7.4
CAN-BD	Carbon Dioxide Assisted-Nebulization with a Bubble Dryer
DELOS	Depressurization of an Expanded Liquid Organic Solution
DSC	Differential Scanning Calorimetry
Ee	Encapsulation Efficiency
FT-IR	Fourier Transform Infrared
GAMA	Gas-Assisted Melting Atomization
GAS	Gas Anti-Solvent
GIT	Gastrointestinal
ICH	International Conference on Harmonization
LC_{50}	Median Lethal Concentration
LD_{50}	Median Lethal Dose
MCP	Mixture Critical Point

MLNE	Multilayered Nanoemulsion
MRT	Mean Residence Time
P_c	Critical Pressue
$P_{c,mix}$	Critical Pressure of Mixture
PBS	Phosphate Buffered Saline
PCA	Particles by Compressed Anti-Solvent
PDE	Permitted Daily Exposure
PGSS	Particles from Gas-Saturated Solution
PGSS-DRYING	Particles from Gas-Saturated Solutions-Drying
PID	Proportional-Integral-Derivative
PPRGEL	Pressure Reduction of Gas-Expanded Liquids
Q_{5min}	Cumulative Release (5 min)
RESOLV	Rapid Expansion of Supercritical Solution into a Liquid Solvent
RESS	Rapid Expansion of Supercritical Fluids
RESSAS	Rapid Expansion of Supercritical Solution into an Aqueous Solution
RESS-N	Rapid Expansion of Supercritical Solution with a Non-Solvent
RH	Relative Humidity
RTD	Ready-To-Drink
SAA	Supercritical Assisted Atomization
SAILA	Supercritical Assisted Injection in a Liquid Anti-Solvent
SAS	Supercritical Anti-Solvent
SASD	Supercritical CO_2-Assisted Spray Drying
SAS-EM	Supercritical Anti-Solvent Precipitation with Enhanced Mass Transfer

sc-CO_2	Supercritical Carbon Dioxide
SCFs	Supercritical Fluids
SEDS	Solution-Enhanced Dispersion by Supercritical Carbon Dioxide
SEM	Scanning Electron Microscopy
SFEE	Supercritical Fluid Extraction of Emulsions
SGF	Simulated Gastric Fluid
SIF	Simulated Intestinal Fluid
SLF	Simulated Lung Fluid
SLN	Solid Lipid Nanoparticle
SMEDDS	Self-Microemulsifying Drug Delivery System
T_c	Critical Temperature
T_g	Glass Transition Temperature
T_m	Melting Point
T_{max}	Time to Reach Maximum Concentration
$t_{1/2}$	Half-life
$t_{75\%}$	Time (75% Cumulative Release)
$t_{90\%}$	Time to Decay to 90% of Its Original Concentration (Shelf Life)
TGA	Thermogravimetric
VLE	Vapor-Liquid Equilibrium
XRD	X-Ray Diffraction

CHAPTER 1

INTRODUCTION

1.1 Background

Andrographis paniculata (Burm.f.) Wall. ex Nees is a perennial herb that belongs to the family of Acanthaceae. Locally, it is named as "Hempedu Bumi". It is also called as "King of bitters" due to its extremely characteristic bitter taste. It grows widely in tropical area of South East Asia, China, and India for traditional medicine purpose to help against fever, dysentery, diarrhea, inflammation, and sore throat (Wongkittipong et al., 2004).

According to Sareer et al. (2012), more than 80 compounds extracted and isolated from this plant had been reported. Type of compounds ranged from diterpene lactones, to a number of polyphenols such as flavonoids, xanthones, quinic acid, and noriridoids (Xu et al., 2012; Xu and Wang, 2011). The characteristic bitter taste as well as the bioactive properties of this plant are due to presence of diterpene lactones with the most abundant one – andrographolide contributing to most of the plant's bitterness and bioactivities (Sareer et al., 2014).

Notwithstanding, andrographolide of which belongs to Class II of the Biopharmaceutics Classification System (BCS) is a poorly soluble and highly permeable drug (Zhang et al., 2016). Its high permeability to intestinal mucosa is attributed to its hydrophobicity. However, it must first dissolve in gastrointestinal fluids before it permeates intestinal membrane to reach systemic circulation (Miller et al., 2007). The rate limiting step for absorption of Class II drug such as andrographolide will be its solubility and dissolution (Savjani et al., 2012). Common strategies that are used to address low drug solubility are categorized as (a) physical modifications, (b) chemical modifications, and (c) miscellaneous as suggested (Savjani et al., 2012). While certain strategies employed during addressing low drug solubility might result in only either physical or chemical modifications of drug, strategy involves usage of supercritical fluids (SCFs) technology could be able to cater both physical and chemical modifications of poor soluble drug as Yasuji et al. (2008) had suggested that solubility improvement of poor aqueous soluble drug by SCFs was due to drug micronization (physical modification) and composite particle formation (chemical modification), all achievable in one step process.

1.2 Problem Statement

Despite of the therapeutic functions of andrographolide, it has been categorized by the BCS as a poorly soluble and highly permeable drug (Zhang et al., 2016). Solubility is an important parameter to allow the achievement of desired active concentration in systemic circulation for a targeted response, be it a pharmacological response for a drug (Savjani et al., 2012). Poorly soluble drug such as andrographolide will therefore need higher dosage or frequent dosage in order to reach the targeted concentration for a response. In

order to improve its absorption, the aqueous solubility of andrographolide needs to be improved so that it can present in the form of solution (aqueous gastrointestinal fluids) at the site of absorption to be absorbed. However, with improved aqueous solubility, the absorption of andrographolide can still be poor for its low dissolution rate. Andrographolide needs to be readily release from dosage while at the same time to be soluble in fluids in order for absorption. Therefore poor aqueous solubility and poor dissolution rate of andrographolide are both the limiting features for its low oral bioavailability that need to be solved.

1.3 Objectives

(1) To investigate the effect of organic solvents and their mixture at different pressure-temperature combination applied during Solution-Enhanced Dispersion by Supercritical Carbon Dioxide (SEDS) precipitation of *A. paniculata* extract on aqueous solubility of andrographolide.
(2) To investigate the effect of polymers and their core/polymer mass ratio applied in SEDS co-precipitation on dissolution of andrograpolide.
(3) To characterize the SEDS co-precipitates with the best andrographolide dissolution profile in Simulated Intestinal Fluids (SIF), pH 7.4 in terms of andrographolide content, encapsulation efficiency, morphology, crystallinity, thermal stability, core-polymer interaction.
(4) To evaluate the storage stability profile of andrographolide in SEDS co-precipitates after being stressed under different storage temperature.
(5) To evaluate the application stability of andrographolide in SEDS co-precipitates after being added into different Ready-To-Drink (RTD) beverages of different pH, respectively.
(6) To identify the residual solvent content of SEDS co-precipitates and in vivo toxicity of the SEDS co-precipitates in comparison with crude *A. paniculata* extract and SEDS precipitated *A. paniculata* extract powder.

1.4 Thesis Outline

The focus of this study is on improvement of aqueous solubility and dissolution of andrographolide from *A. paniculata* extract using SEDS approach. The rationale of study is as a form of particle engineering to micronize *A. paniculata* extract as well as to co-precipitate *A. paniculata* extract with polymer in order to improve aqueous solubility and dissolution of andrographolide under the target medium. This helps to unlock the therapeutic potential of the medicinal plant - *A. paniculata* as the bioavailability of andrographolide from this plant is often restricted by its poor aqueous solubility and poor dissolution.

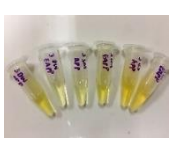
The first working chapter focuses on micronization (precipitation) of sticky lump of *A. paniculata* extract into *A. paniculata* powder form using SEDS approach. It involves the study of effect of organic solvents and their mixture at different pressure-temperature combination applied during SEDS precipitation on aqueous solubility of andrographolide. The precipitation of andrographolide from *A. paniculata* extract can be

modified in view of the different solubility of anti-solvent in solvent that may result in a change of precipitation as well as physical and chemical properties of powder precipitated. The objective is to improve aqueous solubility of andrographolide by increasing surface area of particle as well as by reducing crystallinity of andrographolide precipitated. The type of solvent, SEDS operating pressure and temperature that resulted in precipitation of powder with the highest aqueous solubility of andrographolide will then be applied in the second working chapter.

Co-precipitation of *A. paniculata* extract with polymer is required to unlock the dissolution improvement of andrographolide after the improvement of aqueous solubility of andrographolide through SEDS micronization as shown in the previous chapter. The second working chapter involves study of co-precipitation of *A. paniculata* extract with three different polymers (Pluronic F127, Eudragit EPO, Eudragit L100-55) with the objective to improve dissolution of andrographolide in the target medium by reducing crystallinity of andrographolide. Polymer that can target improved dissolution of andrographolide in SIF, pH 7.4 will be selected for co-precipitation with *A. paniculata* extract in different mass ratios in order to evaluate its concentration effect on andrographolide dissolution in that target environment. Co-precipitates with the highest andrographolide dissolution in SIF, pH 7.4 will be further characterized in terms of its andrographolide content, encapsulation efficiency, thermal and chemical properties.

In the third working chapter, the stability of the andrographolide from the SEDS co-precipitates will be further tested under different stressed storage conditions for two months. The stability of andrographolide from SEDS co-precipitates will also be evaluated after their addition into different pH RTD beverages for three days. This part of study represents the application stability test of SEDS co-precipitates which can provide an insight on how the degradation of andrographolide will vary with time under the presence of food matrix since its targeted application is a food applicable herbal powder (source of andrographolide) for enrichment purpose. The amount of andrographolide remained will be quantified as a way to evaluate the stability of andrographolide from SEDS co-precipitates. Toxicity of the SEDS co-precipitates will be further tested using brine shrimp as the model to identify the lethal concentration (LC_{50}) after the solvent residue test on the SEDS co-precipitates. A study overview is shown in Table 1.1.

Table 1.1: Study overview

	Stage	Rationale	Outcome
1st	Preparation and deposition of voucher specimen (Voucher No. SK 2767/15) in herbarium	Authentication by botanist	Authenticated whole *A. paniculata* plant
2nd	Washing, draining, cutting, drying, grinding	Pre-treatment before extraction	Dried ground whole *A. paniculata* plant powder
3rd	Conventional solid-liquid extraction (Cold Maceration)	Extract obtained as raw material of study	Sticky crude *A. paniculata* extract 
4th	SEDS precipitation of extract	Study precipitation pattern of *A. paniculata* extract, Modification of precipitation (solvent/solvent mixture at different P-T) to improve aqueous solubility	SEDS precipitated *A. paniculata* extract powder with improved aqueous solubility of andrographolide 
5th	SEDS co-precipitation of extract with polymers	Improvement of dissolution of andrographolide with aid of polymers	SEDS co-precipitates with improved dissolution of andrographolide in target medium 
6th	Stability study of SEDS co-precipitates	Storage stability at different temperature, Application stability (after addition of powder into different RTD beverages with different pH	Stable SEDS co-precipitates 
7th	Toxicity study	Solvent residue check on SEDS co-precipitates, Brine shrimp toxicity assay for LC_{50} determination	SEDS co-precipitates with negligible solvent content (< 0.1 ppm) and LC_{50} = 46.46 µg/mL

REFERENCES

Adedapo, A.A., Adeoye, B.O., Oyagbemi, A.A., Omobowale, T.O., Yakubu, M.A., 2017. Cardioprotective effects of the ethanol leaf extract of *Andrographis paniculata* in isoproterenol-induced myocardial infarction in rats. FASEB J. 31, 1070.12.

Adedapo, A.A., Adeoye, B.O., Sofidiya, M.O., Oyagbemi, A.A., 2015. Antioxidant, antinociceptive and anti-inflammatory properties of the aqueous and ethanolic leaf extracts of *Andrographis paniculata* in some laboratory animals. J. Basic Clin. Physio. Pharmacol. 26, 327-334.

Adeli, E., 2016. The use of supercritical anti-solvent (SAS) technique for preparation of Irbesartan-Pluronic®F-127 nanoparticles to improve the drug dissolution. Powder Technol. 298, 65-72.

Adeoye, B.O., Asenuga, E.R., Oyagbemi, A.A., Omobowale, T.O., Adedapo, A.A., 2018. The protective effect of the ethanol leaf extract of *Andrographis paniculata* on cisplatin-induced acute kidney injury in rats through nrf2/KIM-1 signalling pathway. Drug Res. (Stuttg) 68, 23-32.

Akbar, S., 2011. *Andrographis paniculata*: A review of pharmacological activities and clinical effects. Altern. Med. Rev. 16, 66-77.

Akbarsha, M.A., Manivannan, B., Hamid, K.S., Vijayan, B., 1990. Antifertility effect of *Andrographis paniculata* (Nees) in male albino rat. Indian J. Exp. Biol. 28, 421-426.

Akbarsha, M.A., Murugaian, P., 2000. Aspects of the male reproductive toxicity/male antifertility property of andrographolide in albino rats: Effect on the testis and the cauda epididymidal spermatozoa. Phytother. Res. 14, 432-435.

Akhtar, M.T., Bin Mohd Sarib, M.S., Ismail, I.S., Abas, F., Ismail, A., Lajis, N.H., Shaari, K., 2016. Anti-diabetic activity and metabolic changes induced by *Andrographis paniculata* plant extract in obese diabetic rats. Molecules 21, 1026.

Al Batran, R., Al-Bayaty, F., Al-Obaidi, M.M.J., Abdulla, M.A., 2013. Acute toxicity and the effect of andrographolide on *Porphyromonas gingivalis*-induced hyperlipidemia in rats. Biomed Res. Int. 2013, 1-7.

Allan, J.J., Pore, M.P., Deepak, M., Murali, B., Mayachari, A.S., Agarwal, A., 2009. Reproductive and fertility effects of an extract of *Andrographis paniculata* in male Wistar rats. Int. J. Toxicol. 28, 308-317.

Anarjan, N., Tan, C.P., 2013. Chemical stability of astaxanthin nanodispersions in orange juice and skimmed milk as model food systems. Food Chem. 139, 527-531.

Anderson, J.E., Goetz, C.M., McLaughlin, J.L., Suffness, M., 1991. A blind comparison of simple bench-top bioassays and human tumour cell cytotoxicities as antitumor prescreens. Phytochem. Anal. 2, 107-111.

Aresta, M., 2013. Carbon Dioxide Recovery and Utilization, first ed. Kluwer Academic Publishers, Dordrecht.

Armbruster, M., Mönckedieck, M., Scherließ, R., Daniels, R., Wahl, M.A., 2017. Birch bark dry extract by supercritical fluid technology: Extract characterisation and use for stabilisation of semisolid systems. Appl. Sci. 7, 292.

Bakry, A.M., Abbas, S., Ali, B., Majeed, H., Abouelwafa, M.Y., Mousa, A., Liang, L., 2016. Microencapsulation of oils: A comprehensive review of benefits, techniques, and applications. Compr. Rev. Food Sci. Food Saf. 15, 143-182.

Bao, Z., Guan, S., Cheng, C., Wu, S., Wong, S.H., Kemeny, D.M., Leung, B.P., Wong, W.S., 2009. A novel antiinflammatory role for andrographolide in asthma via inhibition of the nuclear factor-kappaB pathway. Am. J. Respir. Crit. Care Med. 179, 657-665.

Bardeau, T., Savoire, R., Cansell, M., Subra-Paternault, P., 2015. Recovery of oils from press cakes by CO_2-based technology. OCL 22, D403.

Bauer, J.F., 2009. Pharmaceutical solids: Size, shape, and surface area. J. Valid. Technol., 37-44.

Benelli, P., Comim, S.R.R., Oliveira, J.V., Pedrosa, R.C., Ferreira, S.R.S., 2014. Phase equilibrium data of guacatonga (*Casearia sylvestris*) extract + ethanol + CO_2 system and encapsulation using a supercritical anti-solvent process. J. Supercrit. Fluids 93, 103-111.

Berenhauser, A.C., Soares, D., Komora, N., De Dea Lindner, J., Schwinden Prudêncio, E., Oliveira, J.V., Block, J.M., 2018. Effect of high-pressure carbon dioxide processing on the inactivation of aerobic mesophilic bacteria and *Escherichia coli* in human milk. CyTA-J. Food 16, 122-126.

Board, N., 2003. Herbs Cultivation & Their Utilization. Asia Pacific Business Press, New Delhi.

Boopathi, C.A., 2000. *Andrographis spp.*: A source of bitter compounds for medicinal use. Anc. Sci. Life 19, 164-168.

Boschetto, D.L., Dalmolin, I., de Cesaro, A.M., Rigo, A.A., Ferreira, S.R.S., Meireles, M.A.A., Batista, E.A.C., Vladimir Oliveira, J., 2013. Phase behavior and process parameters effect on grape seed extract encapsulation by SEDS technique. Ind. Crops Prod. 50, 352-360.

Brooks, A.D., Sanoski, C., Hajjar, E.R., Overholser, B.R., 2017. NAPLEX 2017 Strategies, Practice & Review with 2 Practice Tests: Online + Book. Kaplan Publishing, New York.

Brunner, G., 2000. Fractionation of fats with supercritical carbon dioxide. Eur. J. Lipid Sci. Technol. 102, 240-245.

Burgos, R.A., Caballero, E.E., Sanchez, N.S., Schroeder, R.A., Wikman, G.K., Hancke, J.L., 1997. Testicular toxicity assessment of *Andrographis paniculata* dried extract in rats. J. Ethnopharmacol. 58, 219-224.

Calabrese, C., Berman, S.H., Babish, J.G., Ma, X., Shinto, L., Dorr, M., Wells, K., Wenner, C.A., Standish, L.J., 2000. A phase I trial of andrographolide in HIV positive patients and normal volunteers. Phytother. Res. 14, 333-338.

Campardelli, R., Reverchon, E., 2015. α-Tocopherol nanosuspensions produced using a supercritical assisted process. J. Food Eng. 149, 131-136.

Ceni, G., Fernandes Silva, M., Valério Jr, C., Cansian, R.L., Vladimir Oliveira, J., Dalla Rosa, C., Mazutti, M.A., 2016. Continuous inactivation of alkaline phosphatase and *Escherichia coli* in milk using compressed carbon dioxide as inactivating agent. J. CO_2 Util. 13, 24-28.

Chakraborty, S., Biswas, S., Sa, B., Das, S., Dey, R., 2014. In vitro & in vivo correlation of release behavior of andrographolide from silica and PEG assisted silica gel matrix. Colloids Surf. A Physicochem. Eng. Asp. 455, 111-121.

Chandrasekaran, C.V., Thiyagarajan, P., Sundarajan, K., Goudar, K.S., Deepak, M., Murali, B., Allan, J.J., Agarwal, A., 2009. Evaluation of the genotoxic potential and acute oral toxicity of standardized extract of *Andrographis paniculata* (KalmCold). Food Chem. Toxicol. 47, 1892-1902.

Chang, C.M.J., Day, C.Y., Ko, C.M., Chiu, K.L., 1997. Densities and P-x-y diagrams for carbon dioxide dissolution in methanol, ethanol, and acetone mixtures. Fluid Phase Equilib. 131, 243-258.

Charoenchaitrakool, M., Trisilanun, W., Srinopakhun, P., 2010. Application of gas anti-solvent process to the recovery of andrographolide from *Andrographis paniculatanees*. Korean J. Chem. Eng. 27, 950-954.

Chellampillai, B., Kumbhar, V., Pawar, A., Shaikh, K., Kamble, R., 2015. Development of floating in situ gelling system as an efficient anti-ulcer formulation: In vitro and in vivo studies. RSC Adv. 5, 28848-28856.

Chellampillai, B., Pawar, A.P., 2011a. Andrographolide, a novel bioactive phytoconstituent encapsulated in sustained release biodegradable nanoparticles. Int. J. Nanotechnol. 8, 764-778.

Chellampillai, B., Pawar, A.P., 2011b. Improved bioavailability of orally administered andrographolide from pH-sensitive nanoparticles. Eur. J. Drug Metab. Pharmacokinet. 35, 123-129.

Chellampillai, B., Pawar, A.P., Munde, P.L., Shaikh, K.S., 2012. Preparation, optimization and in-vitro evaluation of andrographolide loaded floating Cavilink beads for phytotherapy. Nanosci. Nanotechnol. Lett. 4, 445-453.

Chellampillai, B., Pawar, A.P., Shaikh, K.S., Sher, P., 2009a. Eudragit® EPO based nanoparticle suspension of andrographolide: In vitro and in vivo. Nanosci. Nanotechnol. Lett. 1, 156-164.

Chellampillai, B., Pawar, A.P., Shende, V.S., Joshi, P.P., 2013. Acute and subacute toxicity study of andrographolide bioactive in rodents: Evidence for the medicinal use as an alternative medicine. Comp. Clin. Path. 22, 1123-1128.

Chellampillai, B., Shinde, M.B., Rajalakshmi, S., Pawar, A.P., 2009b. Evaluation of molecular pharmaceutical and in-vivo properties of spray-dried isolated andrographolide-PVP. J. Pharm. Pharmacol. 61, 1465-1472.

ChemSpider, 2015. CSID:4477067. Royal Society of Chemistry. http://www.chemspider.com/Chemical-Structure.4477067.html/ (accessed 12 April 2018).

Chen, H., Schwartz, S.J., Spanos, G.A., 1992. Fractionation of butter oil by supercritical carbon dioxide. J. Dairy Sci. 75, 2659-2669.

Chen, K., Yin, W., 2009. Effects of entrainers on the purity of andrographolide extracted from andrographolide raw material by SC-CO_2. Sep. Purif. Technol. 70, 207-211.

Chen, K., Zhang, X., Pan, J., Yin, W., 2005. Recrystallization of andrographolide using the supercritical fluid antisolvent process. J. Cryst. Growth 274, 226-232.

Chen, K., Zhang, X., Pan, J., Zhang, W., Yong, J., Yin, W., 2003. Influence of magnetic field on the morphology of the andrographolide crystal from supercritical carbon dioxide extraction–crystallization. J. Cryst. Growth 258, 163-167.

Chen, L., Jin, H., Ding, L., Zhang, H., Wang, X., Wang, Z., Li, J., Qu, C., Wang, Y., Zhang, H., 2007. On-line coupling of dynamic microwave-assisted extraction with high-performance liquid chromatography for determination of andrographolide and dehydroandrographolide in *Andrographis paniculata* Nees. J. Chromatogr. A 1140, 71-77.

Chen, M., Xie, C., Liu, L., 2010. Solubility of andrographolide in various solvents from (288.2 to 323.2)K. J. Chem. Eng. Data 55, 5297-5298.

Chen, X., Zhang, J., Yuan, L., Lay, Y., Wong, Y.K., Lim, T.K., Ong, C.S., Lin, Q., Wang, J., Hua, Z., 2017. Andrographolide suppresses MV4-11 cell proliferation through the inhibition of FLT3 signaling, fatty acid synthesis and cellular iron uptake. Molecules 22, 1444.

Chomcharn, N., Xanthos, M., 2013. Properties of aspirin modified enteric polymer prepared by hot-melt mixing. Int. J. Pharm. 450, 259-267.

Chong, G.H., Yunus, R., Abdullah, N., Choong, T.S.Y., Spotar, S., 2009. Coating and encapsulation of nanoparticles using supercritical antisolvent. Am. J. Appl. Sci. 6, 1352-1358.

Churiyah, Pongtuluran, O.B., Rofaani, E., Tarwadi, 2015. Antiviral and immunostimulant activities of *Andrographis paniculata*. HAYATI J. Biosci. 22, 67-72.

Das, S., Pradhan, G.K., Das, S., Nath, D., Das Saha, K., 2015. Enhanced protective activity of nano formulated andrographolide against arsenic induced liver damage. Chem. Biol. Interact. 242, 281-289.

Day, C.Y., Chang, C.J., Chen, C.Y., 1996. Phase equilibrium of ethanol + CO_2 and acetone + CO_2 at elevated pressures. J. Chem. Eng. Data 41, 839-843.

de Aguiar, A.C., Silva, L.P.S., de Rezende, C.A., Barbero, G.F., Martínez, J., 2016. Encapsulation of pepper oleoresin by supercritical fluid extraction of emulsions. J Supercrit. Fluids 112, 37-43.

De Gioannis, B., Jestin, P., Subra, P., 2004. Morphology and growth control of griseofulvin recrystallized by compressed carbon dioxide as antisolvent. J. Cryst. Growth 262, 519-526.

de Paz, E., Martín, Á., Every, H., Cocero, M.J., 2015. Production of water-soluble quercetin formulations by antisolvent precipitation and supercritical drying. J. Supercrit. Fluids 104, 281-290.

Denardin, F.G., Vieira de Melo, S.A.B., Mammucari, R., Foster, N.R., 2013. Phase transition and volume expansion in CO_2-expanded liquid systems. Chem. Eng. Trans. 32, 529-534.

Deswarte, F.E.I., Clark, J.H., Hardy, J.J.E., Rose, P.M., 2006. The fractionation of valuable wax products from wheat straw using CO_2. Green Chem. 8, 39-42.

Dhore, P.W., Dave, V.S., Saoji, S.D., Gupta, D., Raut, N.A., 2017. Influence of carrier (polymer) type and drug-carrier ratio in the development of amorphous dispersions for solubility and permeability enhancement of ritonavir. J. Excip. Food Chem. 8, 75-92.

Di Capua, A., Bejarano, A., Adami, R., Reverchon, E., 2018. Preparation and characterization of Chilean propolis coprecipitates using supercritical assisted atomization. Chem. Eng. Res. Des. 136, 776-785.

Ding, L., Li, J., Song, B., Xiao, X., Huang, W., Zhang, B., Tang, X., Qi, M., Yang, Q., Yang, Q., Yang, L., Wang, Z., 2014. Andrographolide prevents high-fat diet-induced obesity in C57BL/6 mice by suppressing the sterol regulatory element-binding protein pathway. J. Pharmacol. Exp. Ther. 351, 474-483.

DiNunzio, J.C., Brough, C., Miller, D.A., Williams, R.O., McGinity, J.W., 2010. Applications of KinetiSol dispersing for the production of plasticizer free amorphous solid dispersions. Eur. J. Pharm. Sci. 40, 179-187.

Doi, H., Matsui, T., Ohye, T., Saito, K., Katsuda, I., Akiyama, H., 2017. Andrographolide from the herb *Andrographis paniculata* induces apoptosis on cultured human leukemic cells. Fujita Med. J. 3, 48-54.

Du, H., Yang, X., Li, H., Han, L., Li, X., Dong, X., Zhu, Q., Ye, M., Feng, Q., Niu, X., 2012. Preparation and evaluation of andrographolide-loaded microemulsion. J. Microencapsul. 29, 657-665.

Du, J., Zhang, C., Na, X., Li, A., Zhang, Q., Li, K., Ding, Y., 2018. Andrographolide protects mouse astrocytes against hypoxia injury by promoting autophagy and S100B expression. Braz. J. Med. Biol. Res. 51, 7061.

Duarte, A.R.C., Duarte, C.M.M., 2010. Current Trends of Supercritical Fluid Technology in Pharmaceutical, Nutraceutical and Food Processing Industries. Bentham Science Publishers. Accessed from http://books.google.com.my/books?id=Zv9K5ou0HykC&printsec=frontcover #v=onepage&q&f=false.

Elizondo, E., Sala, S., Imbuluzqueta, E., González, D., Blanco-Prieto, M.J., Gamazo, C., Ventosa, N., Veciana, J., 2011. High loading of gentamicin in bioadhesive PVM/MA nanostructured microparticles using compressed carbon-dioxide. Pharm. Res. 28, 309-321.

EMA, 2014. Assessment report on *Andrographis paniculata* Nees, folium. European Medicines Agency (EMA), London.

Fabroni, S., Amenta, M., Timpanaro, N., Rapisarda, P., 2010. Supercritical carbon dioxide-treated blood orange juice as a new product in the fresh fruit juice market. Innov. Food Sci. Emerg. Technol. 11, 477-484.

Fegus, U., Zigon, U., Petermann, M., Knez, Z., 2015. Effect of drying parameters on physiochemical and sensory properties of fruit powders processed by PGSS-, vacuum- and spray-drying. Acta Chim. Slov. 62, 479-487.

Fiori, L., Manfrini, M., Castello, D., 2014. Supercritical CO_2 fractionation of omega-3 lipids from fish by-products: Plant and process design, modeling, economic feasibility. Food Bioprod. Process. 92, 120-132.

Fraile, M., Buratto, R., Gómez, B., Martín, Á., Cocero, M.J., 2014. Enhanced delivery of quercetin by encapsulation in poloxamers by supercritical antisolvent process. Ind. Eng. Chem. Res. 53, 4318-4327.

Fraile, M., Martín, A., Deodato, D., Rodriguez-Rojo, S., Nogueira, I.D., Simplício, A.L., Cocero, M.J., Duarte, C.M.M., 2013. Production of new hybrid systems for drug delivery by PGSS (particles from gas saturated solutions) process. J. Supercrit. Fluids 81, 226-235.

Friedrich, J.P., 1984. Supercritical CO_2 extraction of lipids from lipid-containing materials, in: Patent, U.S. (Ed.). The United States of America as represented by the Secretary of Agriculture, Washington, D.C.

Gao, H., Wang, J., 2016. Andrographolide inhibits multiple myeloma cells by inhibiting the TLR4/NF-kB signaling pathway. Mol. Med. Rep. 13, 1827-1832.

Girotra, P., Singh, S.K., Nagpal, K., 2013. Supercritical fluid technology: A promising approach in pharmaceutical research. Pharm. Dev. Technol. 18, 22-38.

Globinmed, 2012. Malaysian Herbal Monograph. Global Information Hub on Integrated Medicine(Globinmed). http://www.globinmed.com/index.php?option=com_content&view=article&id=102062:andrographis-paniculata-nees&catid=209&Itemid=143/ (accessed 26 January 2018).

Goodship, V., Ogar, E.O., 2004. Polymer Processing with Supercritical Fluids. Smithers Rapra Press, Shropshire.

Guo, W., Liu, W., Chen, G., Hong, S., Qian, C., Xie, N., Yang, X., Sun, Y., Xu, Q., 2012. Water-soluble andrographolide sulfonate exerts anti-sepsis action in mice through down-regulating p38 MAPK, STAT3 and NF-kB pathways. Int. Immunopharmacol. 14, 613-619.

Gupta, R.B., Kompella, U.B., 2006. Nanoparticle Technology for Drug Delivery, first ed. CRC Press, Boca Raton.

Gupta, S., Mishra, K.P., Dash, P.K., Parida, M., Ganju, L., Singh, S.B., 2018. Andrographolide inhibits chikungunya virus infection by up-regulating host innate immune pathways. Asian Pac. J. Trop. Med. 11, 214-221.

Handa, S.S., Sharma, A., 1990. Hepatoprotective activity of andrographolide from *Andrographis paniculata* against carbontetrachloride. Indian J. Med. Res. 92, 276-283.

Hao, S., Wang, B., Wang, Y., Zhu, L., Wang, B., Guo, T., 2013. Preparation of Eudragit L 100-55 enteric nanoparticles by a novel emulsion diffusion method. Colloids Surf. B Biointerfaces 108, 127-133.

He, G.Q., Xiong, H.P., Chen, Q.H., Ruan, H., Wang, Z.Y., Traore, L., 2005. Optimization of conditions for supercritical fluid extraction of flavonoids from hops (*Humulus lupulus* L.). J. Zhejiang Univ. Sci. B 6, 999-1004.

He, S., Zhou, B., Zhang, S., Lei, Z., Zhang, Z., 2011. Preparation of nanoparticles of Magnolia bark extract by rapid expansion from supercritical solution into aqueous solutions. J. Microencapsul. 28, 183-189.

Higuchi, T., Connors, K.A., 1965. Phase-solubility techniques, in: Reilly, C.N. (Ed.), Advances in Analytical Chemistry and Instrumentation. Wiley-Interscience, New York, pp. 117-212.

Hirasa, K., Takemasa, M., 1998. Spice Science and Technology. Marcel Dekker, New York.

Hsieh, Y.L., Shibu, M.A., Lii, C.K., Viswanadha, V.P., Lin, Y.L., Lai, C.H., Chen, Y.F., Lin, K.H., Kuo, W.W., Huang, C.Y., 2016. *Andrographis paniculata* extract attenuates pathological cardiac hypertrophy and apoptosis in high-fat diet fed mice. J. Ethnopharmacol. 192, 170-177.

Hua, Z., Frohlich, K.M., Zhang, Y., Feng, X., Zhang, J., Shen, L., 2015. Andrographolide inhibits intracellular *Chlamydia trachomatis* multiplication and reduces secretion of proinflammatory mediators produced by human epithelial cells. Pathog. Dis. 73, 1-11.

Huang, Y., Zu, Y., Zhao, X., Wu, M., Feng, Z., Deng, Y., Zu, C., Wang, L., 2016. Preparation of inclusion complex of apigenin-hydroxypropyl-β-cyclodextrin by using supercritical antisolvent process for dissolution and bioavailability enhancement. Int. J. Pharm. 511, 921-930.

Hughey, J.R., DiNunzio, J.C., Bennett, R.C., Brough, C., Miller, D.A., Ma, H., Williams, R.O., McGinity, J.W., 2010. Dissolution enhancement of a drug exhibiting thermal and acidic decomposition characteristics by fusion processing: A comparative study of hot melt extrusion and KinetiSol® dispersing. AAPS PharmSciTech 11, 760-774.

Ibrahim, M.N., Chong, G.H., 2008. Stability of andrographolide in *Andrographis paniculata* under selected storage conditions. Int. J. Eng. Technol. 5, 69-73.

ICH, 2016. ICH guideline Q3C(R6) on impurities: Guideline for residual solvents. International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Switzerland.

Imsanguan, P., Pongamphai, S., Douglas, S., Teppaitoon, W., Douglas, P.L., 2010. Supercritical antisolvent precipitation of andrographolide from *Andrographis paniculata* extracts: Effect of pressure, temperature and CO_2 flow rate. Powder Technol. 200, 246-253.

Imsanguan, P., Yanothai, T., Pongamphai, S., Douglas, S., Teppaitoon, W., Douglas, P.L., 2011. Precipitation of pharmaceuticals using a supercritical anti-solvent (SAS) dechnique: A preliminary study. Can. J. Chem. Eng. 89, 529-535.

Jacq, K., David, F., Sandra, P., Klee, M.S., 2008. A Generic Method for the Analysis of Residual Solvents in Pharmaceuticals Using Static Headspace-GC-FID/MS. Agilent Technologies, Inc., United States, pp. 1-12.

Jain, D.C., Gupta, M.M., Saxena, S., Kumar, S., 2000. LC analysis of hepatoprotective diterpenoids from *Andrographis paniculata*. J. Pharm. Biomed. Anal. 22, 705-709.

Jain, P.K., Khurana, N., Pounikar, Y., Gajbhiye, A., Kharya, M.D., 2013. Enhancement of absorption and hepatoprotective potential through soya-phosphatidylcholine-andrographolide vesicular system. J. Liposome Res. 23, 110-118.

Jarmer, D.J., Lengsfeld, C.S., Anseth, K.S., Randolph, T.W., 2005. Supercritical fluid crystallization of griseofulvin: Crystal habit modification with a selective growth inhibitor. J. Pharm. Sci. 94, 2688-2702.

Jiang, Y., Wang, F., Xu, H., Liu, H., Meng, Q., Liu, W., 2014. Development of andrographolide loaded PLGA microspheres: optimization, characterization and in vitro-in vivo correlation. Int. J. Pharm. 475, 475-484.

Kakran, M., Sahoo, N.G., Antipina, M.N., Li, L., 2013. Modified supercritical antisolvent method with enhanced mass transfer to fabricate drug nanoparticles. Mater. Sci. Eng. C Mater. Biol. Appl. 33, 2864-2870.

Kale, R.S., Bahekar, S.E., Nagpure, S.R., Salwe, K.J., 2013. Anti-scorpion venom activity of *Andrographis paniculata*: A combined and comparative study with anti-scorpion serum in mice. Anc. Sci. Life 32, 156-160.

Kalogiannis, C.G., Pavlidou, E., Panayiotou, C.G., 2005. Production of amoxicillin microparticles by supercritical antisolvent precipitation. Ind. Eng. Chem. Res. 44, 9339-9346.

Kamaruzaman, K.A., Mat Noor, M., 2017. Reversible spermatoxic effect of *Andrographis paniculata* methanol extract in Sprague Dawley rats. Malays. Appl. Biol. 46, 225-232.

Kang, Y.Q., Zhao, C., Chen, A.Z., Wang, S.B., Liu, Y.G., Wu, W.G., Su, X.Q., 2013. Study of lysozyme-loaded Poly-L-Lactide (PLLA) porous microparticles in a compressed CO_2 antisolvent process. Materials 6, 3571-3583.

Karpakavalli, M., Sini, K.R., Arthi, I., 2012. Microwave assisted extraction and estimation of piperine, andrographolide using HPLC techniques. Pharmacie Globale 3, 1-5.

Kim, M.S., Kim, J.S., Hwang, S.J., 2010. Enhancement of wettability and dissolution properties of cilostazol using the supercritical antisolvent process: Effect of various additives. Chem. Pharm. Bull. 58, 230-233.

Kordikowski, A., Schenk, A.P., Van Nielen, R.M., Peters, C.J., 1995. Volume expansions and vapor-liquid equilibria of binary mixtures of a variety of polar solvents and certain near-critical solvents. J. Supercrit. Fluids 8, 205-216.

Kulyal, P., Tiwari, U.K., Shukla, A., Gaur, A.K., 2010. Chemical constituents isolated from *Andrographis paniculata*. Indian J. Chem. 49, 356-359.

Kumar, S., Dhanani, T., Shah, S., 2014. Extraction of three bioactive diterpenoids from *Andrographis paniculata*: Effect of the extraction techniques on extract composition and quantification of three andrographolides using high-performance liquid chromatography. J. Chromatogr. Sci. 52, 1043-1050.

Kumarapppan, C., Jaswanth, A., Kumarasunderi, K., 2011. Antihaemolytic and snake venom neutralizing effect of some Indian medicinal plants. Asian Pac. J. Trop. Med. 4, 743-747.

Kumoro, A.C., Hasan, M., 2007. Supercritical carbon dioxide extraction of andrographolide from *Andrographis paniculata*: Effect of the solvent flow rate, pressure, and temperature. Chin. J. Chem. Eng. 15, 877-883.

Kunastitchai, S., Pichert, L., Sarisuta, N., Müller, B.W., 2006. Application of aerosol solvent extraction system (ASES) process for preparation of liposomes in a dry and reconstitutable form. Int. J. Pharm. 316, 93-101.

Kurian, A., Sankar, M.A., 2007. Medicinal Plants. New India Publishing Agency, India.

Kurniawansyah, F., Quachie, L., Mammucari, R., Foster, N.R., 2017. Improving the dissolution properties of curcumin using dense gas antisolvent technology. Int. J. Pharm. 521, 239-248.

Laboureur, L., Ollero, M., Touboul, D., 2015. Lipidomics by supercritical fluid chromatography. Int. J. Mol. Sci. 16, 13868-13884.

Laddha, K.S., Gavit, R.S., Bhandare, R.R., 2010. Effect of enzymes on extraction of andrographolide from *Andrographis paniculata* Nees. Int. J. Pharma Bio Sci. 1, 1-7.

Lan, T., Wu, T., Gou, H., Zhang, Q., Li, J., Qi, C., He, X., Wu, P., Wang, L., 2013. Andrographolide suppresses high glucose-induced fibronectin expression in mesangial cells via inhibiting the AP-1 pathway. J. Cell. Biochem. 114, 2562-2568.

Lee, S., Nam, K., Kim, M.S., Jun, S.W., Park, J.S., Woo, J.S., Hwang, S.J., 2005. Preparation and characterization of solid dispersions of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. Arch. Pharm. Res. 28, 866-874.

Lee, S.Y., Abdullah, L.C., Abdul Rahman, R., Abas, F., Tan, W.K., Chong, G.H., 2018. Solution enhanced dispersion by supercritical fluids (SEDS): An approach in particle engineering to modify aqueous solubility of andrographolide from *Andrographis paniculata* extract. Chem. Eng. Res. Des. 138, 176-189.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47-60.

Li, B., Konecke, S., Wegiel, L.A., Taylor, L.S., Edgar, K.J., 2013. Both solubility and chemical stability of curcumin are enhanced by solid dispersion in cellulose derivative matrices. Carbohydr. Polym. 98, 1108-1116.

Li, G., Chu, J., Song, E.S., Row, K.H., Lee, K.H., Lee, Y.W., 2006. Crystallization of acetaminophen micro-particle using supercritical carbon dioxide. Korean J. Chem. Eng. 23, 482-487.

Liang, H.X., Lu, S.S., Yan, Z., Kuang, Y.P., Zhu, X.X., Yan, Z.G., Du, T., Chai, W.R., Long, H., Lyu, Q.F., 2017. Andrographolide disrupts meiotic maturation by blocking cytoskeletal reorganisation and decreases the fertilisation potential of mouse oocytes. Reprod. Fertil. Dev. 29, 2336-2344.

Lim, R.T.Y., Ng, W.K., Tan, R.B.H., 2010. Amorphization of pharmaceutical compound by co-precipitation using supercritical anti-solvent (SAS) process (Part I). J. Supercrit. Fluids 53, 179-184.

Liu, Y., Zhang, Y., Zou, J., Yan, L., Yu, X., Lu, P., Wu, X., Li, Q., Gu, R., Zhu, D., 2017. Andrographolide induces autophagic cell death and inhibits invasion and

metastasis of human osteosarcoma cells in an autophagy-dependent manner. Cell. Physiol. Biochem. 44, 1396-1410.

Lomlim, L., Jirayupong, N., Plubrukarn, A., 2003. Heat-accelerated degradation of solid-state andrographolide. Chem. Pharm. Bull. (Tokyo) 51, 24-26.

Lu, W.J., Lee, J.J., Chou, D.S., Jayakumar, T., Fong, T.H., Hsiao, G., Sheu, J.R., 2011. A novel role of andrographolide, an NF-kappa B inhibitor, on inhibition of platelet activation: The pivotal mechanisms of endothelial nitric oxide synthase/cyclic GMP. J. Mol. Med. (Berl) 89, 1261-1273.

Lu, W.J., Lin, K.H., Hsu, M.J., Chou, D.S., Hsiao, G., Sheu, J.R., 2012. Suppression of NF-kB signaling by andrographolide with a novel mechanism in human platelets: Regulatory roles of the p38 MAPK-hydroxyl radical-ERK2 cascade. Biochem. Pharmacol. 84, 914-924.

Lumia, G., Perre, C., Aracil, J., 2007. Method for treating and extracting cork organic compounds, with a dense fluid under pressure, in: Patent, U.S. (Ed.). Commissariat a l'Energie Atomique, Paris, France; Sabate SA., Ceret, France.

Maiti, K., Mukherjee, K., Murugan, V., Saha, B.P., Mukherjee, P.K., 2010. Enhancing bioavailability and hepatoprotective activity of andrographolide from *Andrographis paniculata*, a well-known medicinal food, through its herbosome. J. Sci. Food Agric. 90, 43-51.

Mamatha, A., 2014. Brine shrimp lethality test of *Andrographis paniculata*. Res. J. Pharm. Technol. 7, 743-745.

Martín, A., Mattea, F., Gutiérrez, L., Miguel, F., Cocero, M.J., 2007. Co-precipitation of carotenoids and bio-polymers with the supercritical anti-solvent process. J. Supercrit. Fluids 41, 138-147.

Martin, A., Varona, S., Navarrete, A., Cocero, M.J., 2010. Encapsulation and co-precipitation processes with supercritical fluids: Applications with essential oils. Open Chem. Eng. J. 4, 31-41.

Medsafe, 2017. *Andrographis paniculata* - potential risk for allergic reactions. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe). http://www.medsafe.govt.nz/safety/EWS/2017/AndrographisPaniculata.asp/ (accessed 25 January 2018).

Meng, D., Falconer, J., Krauel-Goellner, K., Chen, J.J.J., Farid, M., Alany, R.G., 2008. Self-built supercritical CO_2 anti-solvent unit design, construction and operation using carbamazepine. AAPS PharmSciTech 9, 944-952.

Meyer, B.N., Ferrigni, N.R., Putnam, J.E., Jacobsen, L.B., Nichols, D.E., McLaughlin, J.L., 1982. Brine shrimp: A convenient general bioassay for active plant constituents. Planta Med. 45, 31-34.

Meziani, M.J., Pathak, P., Sun, Y.P., 2009. Supercritical fluid technology for nanotechnology in drug delivery, in: de Villiers, M.M., Aramwit, P., Kwon, G.S. (Eds.), Nanotechnology in Drug Delivery. Springer New York, pp. 69-104.

Mezzomo, N., Oliveira, D.A., Comim, S.R.R., Ferreira, S.R.S., 2016. Encapsulation of extract from winery industry residue using the supercritical anti-solvent technique Braz. J. Chem. Eng. 33, 589-598.

Miao, H., Chen, Z., Xu, W., Wang, W., Song, Y., Wang, Z., 2018. Preparation and characterization of naringenin microparticles via a supercritical anti-solvent process. J. Supercrit. Fluids 131, 19-25.

Miller, D.A., McGinity, J.W., Williams III, R.O., 2007. Solid dispersion technologies, in: Williams III, R.O., Taft, D.R., McConville, J.T. (Eds.), Advanced Drug Formulation Design to Optimize Therapeutic Outcomes, 1st ed. CRC Press, Boca Raton, pp. 451-454.

Mishra, K., Dash, A.P., Dey, N., 2011. Andrographolide: A novel antimalarial diterpene lactone compound from *Andrographis paniculata* and its interaction with curcumin and artesunate. J. Trop. Med. 2011, 579518.

Mishra, N., Yadav, K.S., Rai, V.K., Yadav, N.P., 2017. Polysaccharide encrusted multilayered nano-colloidal system of andrographolide for improved hepatoprotection. AAPS PharmSciTech 18, 381-392.

Mishra, S., Tiwari, S.K., Kakkar, A., Pandey, A.K., 2010. Chemoprofiling of *Andrographis paniculata* (Kalmegh) for its andrographolide content in Madhya Pradesh, India. Int. J. Pharma Bio Sci. 1, PS78.

Mishra, S.P., Gaikar, V.G., 2006. Aqueous hydrotropic solution as an efficient solubilizing agent for andrographolide from *Andrographis paniculata* leaves. Sep. Sci. Technol. 41, 1115-1134.

Mohd Shukri, M.A., Razali, M., Khozirah, S., Norlia, Y., Mohamed Senawi, M.T., Abdul Ghani, I., 2005. Determination of andrographolide and neoandrographolide levels in hempedu bumi (*Andrographis paniculata* Nees) grown under rubber ecosystem. J. Trop. Agric. and Fd. Sci. 33, 303-309.

Mondal, S., Roy, P., Das, S., Halder, A., Mukherjee, A., Bera, T., 2013. In vitro susceptibilities of wild and drug resistant *Leishmania donovani* amastigote stages to andrographolide nanoparticle: Role of vitamin E derivative TPGS for nanoparticle efficacy. PloS one 8, e81492.

Montes, A., Gordillo, M.D., Pereyra, C., de la Ossa, E.J.M., 2011. Co-precipitation of amoxicillin and ethyl cellulose microparticles by supercritical antisolvent process. J. Supercrit. Fluids 60, 75-80.

Montes, A., Kin, N., Gordillo, M.D., Pereyra, C., de la Ossa, E.J.M., 2014. Polymer–naproxen precipitation by supercritical antisolvent (SAS) process. J. Supercrit. Fluids 89, 58-67.

Montes, A., Wehner, L., Pereyra, C., de la Ossa, E.J.M., 2016. Generation of microparticles of ellagic acid by supercritical antisolvent process. J. Supercrit. Fluids 116, 101-110.

Moshi, M.J., Innocent, E., Magadula, J.J., Otieno, D.F., Weisheit, A., Mbabazi, P.K., Nondo, R.S., 2010. Brine shrimp toxicity of some plants used as traditional medicines in Kagera Region, north western Tanzania. Tanzan. J. Health Res. 12, 63-67.

Mukhopadhyay, M., 2000. Natural Extracts Using Supercritical Carbon Dioxide. CRC Press, Boca Raton.

Naik, S.R., Hule, A., 2009. Evaluation of immunomodulatory activity of an extract of andrographolides from *Andographis paniculata*. Planta Med. 75, 785-791.

NIH, 1993. Andrographolide (RN: 5508-58-7). U.S. National Library of Medicine, United States. http://chem.nlm.nih.gov/chemidplus/rn/5508-58-7/ (accessed 17 October 2017).

Nitave, S.A., Chougule, N.B., Koumaravelou, K., 2018. Phytochemical investigation, analgesic and antipyretic activities of ethanolic extract of Kariyat. Int. J. Pharm. Sci. Res. 9, 1035-1043.

Nuchuchua, O., Every, H.A., Hofland, G.W., Jiskoot, W., 2014. Scalable organic solvent free supercritical fluid spray drying process for producing dry protein formulations. Eur. J. Pharm. Biopharm. 88, 919-930.

Nugroho, A.E., Andrie, M., Warditiani, N.K., Siswanto, E., Pramono, S., Lukitaningsih, E., 2012. Antidiabetic and antihiperlipidemic effect of *Andrographis paniculata* (Burm. f.) Nees and andrographolide in high-fructose-fat-fed rats. Indian J. Pharmacol. 44, 377-381.

Nugroho, A.E., Rais, I.R., Setiawan, I., Pratiwi, P.Y., Hadibarata, T., Tegar, M., Pramono, S., 2014. Pancreatic effect of andrographolide isolated from *Andrographis paniculata* (Burm. f.) Nees. Pak. J. Biol. Sci. 17, 22-31.

Onoue, S., Takahashi, H., Kawabata, Y., Seto, Y., Hatanaka, J., Timmermann, B., Yamada, S., 2010. Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. J. Pharm. Sci. 99, 1871-1881.

Panossian, A., Hovhannisyan, A., Mamikonyan, G., Abrahamian, H., Hambardzumyan, E., Gabrielian, E., Goukasova, G., Wikman, G., Wagner, H., 2000. Pharmacokinetic and oral bioavailability of andrographolide from *Andrographis paniculata* fixed combination Kan Jang in rats and human. Phytomedicine 7, 351-364.

Panraksa, P., Ramphan, S., Khongwichit, S., Smith, D.R., 2017. Activity of andrographolide against dengue virus. Antiviral Res. 139, 69-78.

Parasher, R., Upadhyay, A., Khan, N.A., Dwivedi, S.K., 2011. Biochemical estimation and quantitative determination of medicinally important andrographolide in *Andrographis peniculata* at different growth stages. Electron. J. Environ. Agric. Food Chem. 10, 2479-2486.

Parveen, R., Ahmad, F.J., Iqbal, Z., Samim, M., Ahmad, S., 2014. Solid lipid nanoparticles of anticancer drug andrographolide: Formulation, in vitro and in vivo studies. Drug Dev. Ind. Pharm. 40, 1206-1212.

Pasquali, I., Bettini, R., 2008. Are pharmaceutics really going supercritical? Int. J. Pharm. 364, 176-187.

Patil, M.P., Gaikwad, N.J., 2009. Preparation and characterization of gliclazide-polyethylene glycol 4000 solid dispersions. Acta Pharm. 59, 57-65.

Pawar, A.P., Bothiraja, C., Shinde, M.B., Mahadik, K.R., 2009. Preparation and evaluation of andrographolide solid dispersion by spray drying technique. Indian J. Pharm. Sci. 71, 157.

Pereda, S., Bottini, S.B., Brignole, E.A., 2007. Fundamentals of supercritical fluid technology, in: Martinez, J.L. (Ed.), Supercritical Fluid Extraction of Nutraceuticals and Bioactive Compounds. CRC Press, Boca Raton, pp. 1-24.

Pholphana, N., Rangkadilok, N., Thongnest, S., Ruchirawat, S., Ruchirawat, M., Satayavivad, J., 2004. Determination and variation of three active diterpenoids in *Andrographis paniculata* (Burm.f.) Nees. Phytochem. Anal. 15, 365-371.

Plubrukarn, A., Pinsuwan, S., Ingkatawornwong, S., Supavita, T., 2006. Stability of andrographolide in powdered *Andrographis* herb under accelerated conditions. Planta Med. 72, 954-956.

Prajapati, N.D., 2003. A Handbook of Medicinal Plants: A Complete Source Book. Agrobios, Jodhpur.

Prasad, R., Patsariya, R., Dalvi, S.V., 2017. Precipitation of curcumin by pressure reduction of CO_2-expanded acetone. Powder Technol. 310, 143-153.

Premanath, R., Nanjaiah, L., 2015. Antidiabetic and antioxidant potential of *Andrographis paniculata* Nees. leaf ethanol extract in streptozotocin induced diabetic rats. J. Appl. Pharm. Sci. 5, 69-76.

Proctor, A., 2018. Alternatives to Conventional Food Processing. Royal Society of Chemistry, Cambridge.

Prosapio, V., De Marco, I., Reverchon, E., 2016a. PVP/corticosteroid microspheres produced by supercritical antisolvent coprecipitation. Chem. Eng. J. 292, 264-275.

Prosapio, V., Reverchon, E., De Marco, I., 2015. Coprecipitation of Polyvinylpyrrolidone/β-Carotene by supercritical antisolvent processing. Ind. Eng. Chem. Res. 54, 11568-11575.

Prosapio, V., Reverchon, E., De Marco, I., 2016b. Formation of PVP/nimesulide microspheres by supercritical antisolvent coprecipitation. J. Supercrit. Fluids 118, 19-26.

Ramachandran, S., Vamsikrishna, M., Gowthami, K.V., Heera, B., Dhanaraju, M.D., 2011. Assessment of cytotoxic activity of *Agave cantula* using brine shrimp (*Artemia salina*) lethality bioassay. Asian J. Sci. Res. 4, 90-94.

Rawson, A., Tiwari, B.K., Brunton, N., Brennan, C., Cullen, P.J., O'Donnell, C.P., 2012. Application of supercritical carbon dioxide to fruit and vegetables: Extraction, processing, and preservation. Food Rev. Int. 28, 253-276.

Ren, K., Zhang, Z., Li, Y., Liu, J., Zhao, D., Zhao, Y., Gong, T., 2009. Physicochemical characteristics and oral bioavailability of andrographolide complexed with hydroxypropyl-beta-cyclodextrin. Pharmazie 64, 515-520.

Reverchon, E., Adami, R., Caputo, G., De Marco, I., 2008. Spherical microparticles production by supercritical antisolvent precipitation: Interpretation of results. J. Supercrit. Fluids 47, 70-84.

Reverchon, E., De Marco, I., 2011. Mechanisms controlling supercritical antisolvent precipitate morphology. Chem. Eng. J. 169, 358-370.

Richard, E.J., Murugan, S., Bethapudi, B., Illuri, R., Mundkinajeddu, D., Chinampudur Velusami, C., 2017. Is *Andrographis paniculata* extract and andrographolide anaphylactic? Toxicol. Rep. 4, 431-437.

Rithwan, F., Zhari, S., Che Yunus, M.A., Mohd Hadzri, H., 2014. Efficacy of biological activity of *Andrographis paniculata* extracted by using supercritical CO_2 extraction. J. Teknol. 69, 61-64.

Roselius, W., Vitzthum, O., Hubert, P., 1974. Method for the production of caffeine-free coffee extract, in: Patent, U.S. (Ed.). HAG Aktiengesellschaft, Bremen, Germany.

Rossmann, M., Braeuer, A., Leipertz, A., Schluecker, E., 2013. Manipulating the size, the morphology and the polymorphism of acetaminophen using supercritical antisolvent (SAS) precipitation. J. Supercrit. Fluids 82, 230-237.

Roy, P., Das, S., Auddy, R.G., Mukherjee, A., 2014. Engineered andrographolide nanosystems for smart recovery in hepatotoxic conditions. Int. J. Nanomedicine 9, 4723-4735.

Roy, P., Das, S., Auddy, R.G., Saha, A., Mukherjee, A., 2013. Engineered andrographolide nanoparticles mitigate paracetamol hepatotoxicity in mice. Pharm. Res. 30, 1252-1262.

Roy, P., Das, S., Bera, T., Mondol, S., Mukherjee, A., 2010. Andrographolide nanoparticles in leishmaniasis: Characterization and in vitro evaluations. Int. J. Nanomedicine 5, 1113-1121.

Roy, P., Das, S., Mondal, A., Chatterji, U., Mukherjee, A., 2012. Nanoparticle engineering enhances anticancer efficacy of andrographolide in MCF-7 cells and mice bearing EAC. Curr. Pharm. Biotechnol. 13, 2669-2681.

Salama, R., Sattayasai, J., Gande, A.K., Sattayasai, N., Davis, M., Lattmann, E., 2012. Identification and evaluation of agents isolated from traditionally used herbs against *Ophiophagus hannah* venom. Drug Discov. Ther. 6, 18-23.

Salleh, L.M., Hartati, Jamaludin, R., Che Yunus, M.A., Yakub, H., Aziz, A.A., 2014. Antioxidant activity and total phenolic contents in methanol extracts from *Swietenia mahagoni* and *Andrographis paniculata*. J. Teknol. 69, 51-53.

Salmaso, S., Elvassore, N., Bertucco, A., Caliceti, P., 2009. Production of solid lipid submicron particles for protein delivery using a novel supercritical gas-assisted melting atomization process. J. Pharm. Sci. 98, 640-650.

Santos, D.T., Albarelli, J.Q., Beppu, M.M., Meireles, M.A.A., 2013. Stabilization of anthocyanin extract from jabuticaba skins by encapsulation using supercritical CO_2 as solvent. Food Res. Int. 50, 617-624.

Santos, D.T., Meireles, M.A.A., 2011. Micronization and encapsulation of functional pigments using supercritical carbon dixoide J. Food Process Eng. 36, 36-49.

Saranya, P., Geetha, A., Selvamathy, S.M., 2011. A biochemical study on the gastroprotective effect of andrographolide in rats induced with gastric ulcer. Indian J. Pharm. Sci. 73, 550-557.

Sareer, O., Ahad, A., Umar, S., 2012. Prophylactic and lenitive effects of *Andrographis paniculata* against common human ailments: An exhaustive and comprehensive reappraisal. J. Pharm. Res. Opin. 2, 138-162.

Sareer, O., Ahmad, S., Umar, S., 2014. *Andrographis paniculata*: A critical appraisal of extraction, isolation and quantification of andrographolide and other active constituents. Nat. Prod. Res. 28, 2081-2101.

Sarmin, N.M., Razali, S.A., Markom, M., 2017. Optimization of microencapsulation of *Citrus hystrix* L. oil sub and supercritical CO_2 using response surface methodology. J. Teknol. 79, 29-40.

Sattayasai, J., Srisuwan, S., Arkaravichien, T., Aromdee, C., 2010. Effects of andrographolide on sexual functions, vascular reactivity and serum testosterone level in rodents. Food Chem. Toxicol. 48, 1934-1938.

Savjani, K.T., Gajjar, A.K., Savjani, J.K., 2012. Drug solubility: Importance and enhancement techniques. ISRN Pharm. 2012, 195727.

Saxena, R.C., Singh, R., Kumar, P., Yadav, S.C., Negi, M.P., Saxena, V.S., Joshua, A.J., Vijayabalaji, V., Goudar, K.S., Venkateshwarlu, K., Amit, A., 2010. A randomized double blind placebo controlled clinical evaluation of extract of *Andrographis paniculata* (KalmCold™) in patients with uncomplicated upper respiratory tract infection. Phytomedicine 17, 178-185.

Schmitz, K.S., 2017. Chapter 15 - Reaction rates and mechanisms, in: Schmitz, K.S. (Ed.), Physical Chemistry: Concepts and Theory. Elsevier, Boston, pp. 695-760.

Serajuddin, A.T., 1999. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 88, 1058-1066.

Sermkaew, N., Ketjinda, W., Boonme, P., Phadoongsombut, N., Wiwattanapatapee, R., 2013. Liquid and solid self-microemulsifying drug delivery systems for improving the oral bioavailability of andrographolide from a crude extract of *Andrographis paniculata*. Eur. J. Pharm. Sci. 50, 459-466.

Shaarani, S., Hamid, S.S., Mohd Kaus, N.H., 2017. The influence of Pluronic F68 and F127 nanocarrier on physicochemical properties, in vitro release, and antiproliferative activity of thymoquinone drug. Pharmacognosy Res. 9, 12-20.

Shen, T., Yang, W.S., Yi, Y.S., Sung, G.H., Rhee, M.H., Poo, H., Kim, M.Y., Kim, K.W., Kim, J.H., Cho, J.Y., 2013. AP-1/IRF-3 targeted anti-inflammatory activity of andrographolide isolated from *Andrographis paniculata*. Evid. Based Complement. Alternat. Med. 2013, 210736.

Shi, J., 2015. Functional Food Ingredients and Nutraceuticals: Processing Technologies, Second ed. CRC Press, Boca Raton.

Shimoda, M., Yamamoto, Y., Cocunubo-Castellanos, J., Yoshimura, T., Miyake, M., Ishikawa, H., Osajima, Y., 2000. Deodorization of fish sauce by continuous-flow extraction with microbubbles of supercritical carbon dioxide. J. Food Sci. 65, 1349-1351.

Shinde, N., Chauhan, A.S., Gupta, S.K., Bodakhe, S.H., Pandey, D.P., 2015. Antifertility studies of curcumin and andrographolide combination in female rats. Asian Pac. J. Reprod. 4, 188-194.

Sievers, R.E., Huang, E.T.S., Villa, J.A., Engling, G., Brauer, P.R., 2003. Micronization of water-soluble or alcohol-soluble pharmaceuticals and model compounds with a low-temperature Bubble Dryer®. J. Supercrit. Fluids 26, 9-16.

Singh, S., Mehta, A., Baweja, S., Ahirwal, L., Mehta, P., 2013. Anticancer activity of *Andrographis paniculata* and *Silybum marianum* of five human cancer cell lines. J. Pharmacol. Toxicol. 8, 42-48.

Sonkaew, P., Sane, A., Suppakul, P., 2012. Antioxidant activities of curcumin and ascorbyl dipalmitate nanoparticles and their activities after incorporation into cellulose-based packaging films. J. Agric. Food Chem. 60, 5388-5399.

Sornpet, B., Potha, T., Tragoolpua, Y., Pringproa, K., 2017. Antiviral activity of five Asian medicinal pant crude extracts against highly pathogenic H5N1 avian influenza virus. Asian Pac. J. Trop. Med. 10, 871-876.

Sosa, M.V., Rodríguez-Rojo, S., Mattea, F., Cismondi, M., Cocero, M.J., 2011. Green tea encapsulation by means of high pressure antisolvent coprecipitation. J. Supercrit. Fluids 56, 304-311.

Sriramaneni, R.N., Yalavarthi, P.R., Nair, R., Ameer, O.Z., Salman, I.M., Sadikun, A., Asmawi, M.Z., 2012. Chronic effects of *Andrographis paniculata* chloroform extract in spontaneously hypertensive rats. J. Pharm. Sci. Res. 4, 1924-1928.

Subramaniam, B., Rajewski, R.A., Snavely, K., 1997. Pharmaceutical processing with supercritical carbon dioxide. J. Pharm. Sci. 86, 885-890.

Subramaniam, S., Hedayathullah Khan, H.B., Elumalai, N., Sudha Lakshmi, S.Y., 2015. Hepatoprotective effect of ethanolic extract of whole plant of *Andrographis paniculata* against CCl4-induced hepatotoxicity in rats. Comp. Clin. Pathol. 24, 1245-1251.

Subramanian, R., Asmawi, M.Z., Sadikun, A., 2008. In vitro alpha-glucosidase and alpha-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. Acta Biochim. Pol. 55, 391-398.

Sule, A., Ahmed, Q.U., Latip, J., Samah, O.A., Omar, M.N., Umar, A., Dogarai, B.B., 2012. Antifungal activity of *Andrographis paniculata* extracts and active principles against skin pathogenic fungal strains in vitro. Pharm. Biol. 50, 850-856.

Sule, A., Ahmed, Q.U., Samah, O.A., Omar, M.N., Hassan, N.M., Kamal, L.Z.M., Yarmo, M.A., 2011. Bioassay guided isolation of antibacterial compounds from *Andrographis paniculata*. Am. J. Appl. Sci. 8, 525-534.

Suresh, K., Goud, N.R., Nangia, A., 2013. Andrographolide: Solving chemical instability and poor solubility by means of cocrystals. Chem. Asian J. 8, 3032-3041.

Suzuki, R., Matsushima, Y., Okudaira, N., Sakagami, H., Shirataki, Y., 2016. Cytotoxic components against human oral squamous cell carcinoma isolated from *Andrographis paniculata*. Anticancer Res. 36, 5931-5935.

Tandya, A., Zhuang, H.Q., Mammucari, R., Foster, N.R., 2016. Supercritical fluid micronization techniques for gastroresistant insulin formulations. J. Supercrit. Fluids 107, 9-16.

Tang, C., Gu, G., Wang, B., Deng, X., Zhu, X., Qian, H., Huang, W., 2014. Design, synthesis, and biological evaluation of andrographolide derivatives as potent hepatoprotective agents. Chem. Biol. Drug Des. 83, 324-333.

Teng, W., Wang, J., Foster, N.R., Wen, N., Zhang, J., 2014. Preparation of Silybin/Poly(vinylpyrrolidone) nanodrugs by using the aerosol solvent extraction system for improving drug solubility. Ind. Eng. Chem. Res. 53, 10519-10524.

TGA, 2015. Safety review of *Andrographis paniculata* and anaphylactic/allergic reactions. Therapeutic Goods Administration, Department of Health, Australia.

Thakur, A.K., Rai, G., Chatterjee, S.S., Kumar, V., 2015. Analgesic and anti-inflammatory activity of *Andrographis paniculata* and andrographolide in diabetic rodents. EC Pharm. Sci. 1, 19-28.

Thingale, A.D., Shaikh, K.S., Channekar, P.R., Galgatte, U.C., Chaudhari, P.D., Bothiraja, C., 2015. Enhanced hepatoprotective activity of andrographolide complexed with a biomaterial. Drug Deliv. 22, 117-124.

Thisoda, P., Rangkadilok, N., Pholphana, N., Worasuttayangkurn, L., Ruchirawat, S., Satayavivad, J., 2006. Inhibitory effect of *Andrographis paniculata* extract and its active diterpenoids on platelet aggregation. Eur. J. Pharmacol. 553, 39-45.

Tian, L., Row, K., 2016. Investigation of physical effects on nanoparticle size in aerosol solvent extraction system. J. Nanoanalysis 3, 39-44.

Tomasko, D.L., Li, H., Liu, D., Han, X., Wingert, M.J., Lee, L.J., Koelling, K.W., 2003. A review of CO_2 applications in the processing of polymers. Ind. Eng. Chem. Res. 42, 6431-6456.

Tu, Y.S., Sun, D.M., Zhang, J.J., Jiang, Z.Q., Chen, Y.X., Zeng, X.H., Huang, D.E., Yao, N., 2014. Preparation and characterisation of andrographolide niosomes and its anti-hepatocellular carcinoma activity. J. Microencapsul. 31, 307-316.

Tung, Y.T., Chen, H.L., Tsai, H.C., Yang, S.H., Chang, Y.C., Chen, C.M., 2013. Therapeutic potential of andrographolide isolated from the leaves of *Andrographis paniculata* Nees for treating lung adenocarcinomas. Evid. Based Complement. Alternat. Med. 2013, 305898.

Vasu, S., Palaniyappan, V., Badami, S., 2010. A novel microwave-assisted extraction for the isolation of andrographolide from *Andrographis paniculata* and its in vitro antioxidant activity. Nat. Prod. Res. 24, 1560-1567.

Visentin, A., Rodríguez-Rojo, S., Navarrete, A., Maestri, D., Cocero, M.J., 2012. Precipitation and encapsulation of rosemary antioxidants by supercritical antisolvent process. J. Food Eng. 109, 9-15.

Vitzthum, O., Hubert, P., 1979. Method for the manufacture of caffeine free black tea, in: Patent, U.S. (Ed.). Vitzthum, O., Hubert, P.

Vitzthum, O., Hubert, P., Sirtl, W., 1978. Production of hop extracts, in: Patent, U.S. (Ed.). Studiengesellschaft Kohle mbH, Milheim (Ruhr), Germany.

Wang, H.C., Tsay, H.S., Shih, H.N., Chen, Y.A., Chang, K.M., Agrawal, D.C., Huang, S., Lin, Y.L., Lee, M.J., 2018. Andrographolide relieved pathological pain generated by spared nerve injury model in mice. Pharm. Biol. 56, 124-131.

Wen, Z., Liu, B., Zheng, Z., You, X., Pu, Y., Li, Q., 2010. Preparation of liposomes entrapping essential oil from *Atractylodes macrocephala* Koidz by modified RESS technique. Chem. Eng. Res. Des. 88, 1102-1107.

WHO, 2004. WHO Monographs on Selected Medicinal Plants. Human Info NGO. http://apps.who.int/medicinedocs/en/d/Js4927e/4.html/ (accessed 30 January 2018).

WHO, 2017. WHO Pharmaceuticals Newsletter. World Health Organization (WHO), Switzerland.

Widjojokusumo, E., Veriansyah, B., Youn, Y.S., Lee, Y.W., Tjandrawinata, R.R., 2013. Co-precipitation of loperamide hydrochloride and polyethylene glycol using aerosol solvent extraction system. Korean J. Chem. Eng. 30, 1797-1803.

Williams, H.D., Trevaskis, N.L., Charman, S.A., Shanker, R.M., Charman, W.N., Pouton, C.W., Porter, C.J., 2013. Strategies to address low drug solubility in discovery and development. Pharmacol. Rev. 65, 315-499.

Wintachai, P., Kaur, P., Lee, R.C.H., Ramphan, S., Kuadkitkan, A., Wikan, N., Ubol, S., Roytrakul, S., Chu, J.J.H., Smith, D.R., 2015. Activity of andrographolide against chikungunya virus infection. Sci. Rep. 5, 14179.

Wongkittipong, R., Prat, L., Damronglerd, S., Gourdon, C., 2004. Solid-liquid extraction of andrographolide from plants-experimental study, kinetic reaction and model. Sep. Purif. Technol. 40, 147-154.

Wu, K., Li, J., Wang, W., Winstead, D.A., 2009. Formation and characterization of solid dispersions of piroxicam and polyvinylpyrrolidone using spray drying and precipitation with compressed antisolvent. J. Pharm. Sci. 98, 2422-2431.

Wu, Q.Q., Ni, J., Zhang, N., Liao, H.H., Tang, Q.Z., Deng, W., 2017. Andrographolide protects against aortic banding-induced experimental cardiac hypertrophy by inhibiting MAPKs signaling. Front. Pharmacol. 8, 808.

Xu, C., Chou, G.X., Wang, C.H., Wang, Z.T., 2012. Rare noriridoids from the roots of *Andrographis paniculata*. Phytochemistry 77, 275-279.

Xu, C., Wang, Z.T., 2011. Chemical constituents from roots of *Andrographis paniculata*. Yao Xue Xue Bao 46, 317-321.

Xu, J., Luo, K.Q., 2014. Enhancing the solubility and bioavailability of isoflavone by particle size reduction using a supercritical carbon dioxide-based precipitation process. Chem. Eng. Res. Des. 92, 2542-2549.

Yang, T., Sheng, H.H., Feng, N.P., Wei, H., Wang, Z.T., Wang, C.H., 2013a. Preparation of andrographolide-loaded solid lipid nanoparticles and their in vitro and in vivo evaluations: Characteristics, release, absorption, transports, pharmacokinetics, and antihyperlipidemic activity. J. Pharm. Sci. 102, 4414-4425.

Yang, T., Shi, H.X., Wang, Z.T., Wang, C.H., 2013b. Hypolipidemic effects of andrographolide and neoandrographolide in mice and rats. Phytother. Res. 27, 618-623.

Yasuji, T., Takeuchi, H., Kawashima, Y., 2008. Particle design of poorly water-soluble drug substances using supercritical fluid technologies. Adv. Drug Deliv. Rev. 60, 388-398.

Ye, L., Wang, T., Tang, L., Liu, W., Yang, Z., Zhou, J., Zheng, Z., Cai, Z., Hu, M., Liu, Z., 2011. Poor oral bioavailability of a promising anticancer agent andrographolide is due to extensive metabolism and efflux by P-glycoprotein. J. Pharm. Sci. 100, 5007-5017.

Yen, C.C., Chen, Y.C., Wu, M.T., Wang, C.C., Wu, Y.T., 2018. Nanoemulsion as a strategy for improving the oral bioavailability and anti-inflammatory activity of andrographolide. Int. J. Nanomedicine 13, 669-680.

Yesil-Celiktas, O., Cetin-Uyanikgil, E.O., 2012. In vitro release kinetics of polycaprolactone encapsulated plant extract fabricated by supercritical antisolvent process and solvent evaporation method. J. Supercrit. Fluids 62, 219-225.

York, P., Kompella, U.B., Shekunov, B.Y., 2004. Supercritical Fluid Technology for Drug Product Development. Marcel Dekker, New York.

Yun, J.H., Haque, A.S.M.T., Chun, B.S., 2014. Characterization of wheat germ oil particles formed by gas-saturated solutions process with polyethylene glycol. J. Food Process. Preserv. 39, 1720-1728.

Zahran, F., Cabañas, A., Cheda, J.A.R., Renuncio, J.A.R., Pando, C., 2014. Dissolution rate enhancement of the anti-inflammatory drug diflunisal by coprecipitation with a biocompatible polymer using carbon dioxide as a supercritical fluid antisolvent. J. Supercrit. Fluids 88, 56-65.

Zaid, O.I., Abd Majid, R., Sabariah, M.N., Hasidah, M.S., Al-Zihiry, K., Yam, M.F., Basir, R., 2015. Andrographolide effect on both *Plasmodium falciparum* infected and non infected RBCs membranes. Asian Pac. J. Trop. Med. 8, 507-512.

Zein, U., Fitri, L.E., Saragih, A., 2013. Comparative study of antimalarial effect of sambiloto (*Andrographis paniculata*) extract, chloroquine and artemisinin and their combination against *Plasmodium falciparum* in-vitro. Acta Med. Indones. 45, 38-43.

Zeng, M., Jiang, W., Tian, Y., Hao, J., Cao, Z., Liu, Z., Fu, C., Zhang, P., Ma, J., 2017. Andrographolide inhibits arrhythmias and is cardioprotective in rabbits. Oncotarget 8, 61226-61238.

Zhang, D., Lin, J., Zhang, F., Han, X., Han, L., Yang, M., Zou, W., 2016. Preparation and evaluation of andrographolide solid dispersion vectored by silicon dioxide. Pharmacogn. Mag. 12, 245-252.

Zhang, J., Li, Y., Gao, W., Repka, M.A., Wang, Y., Chen, M., 2014. Andrographolide-loaded PLGA-PEG-PLGA micelles to improve its bioavailability and anticancer efficacy. Expert Opin. Drug Deliv. 11, 1367-1380.

Zhang, J., Zhang, M., Ji, J., Fang, X., Pan, X., Wang, Y., Wu, C., Chen, M., 2015a. Glycyrrhetinic acid-mediated polymeric drug delivery targeting the acidic microenvironment of hepatocellular carcinoma. Pharm. Res. 32, 3376-3390.

Zhang, T., Zhu, L., Li, M., Hu, Y., Zhang, E., Jiang, Q., Han, G., Jin, Y., 2017. Inhalable andrographolide-beta-cyclodextrin inclusion complexes for treatment of *Staphylococcus aureus* pneumonia by regulating immune responses. Mol. Pharm. 14, 1718- 1725.

Zhang, W., Pan, J., 2005. Study on purifying technology of andrographolide by supercritical carbon dioxide secondary gradient crystallization. Zhongguo Nongye Kexue (China) 38, 140-144.

Zhang, W.C., Xie, H.M., 2007. Solubilities of andrographolide in supercritical CO_2. Food Sci. 28, 32-34.

Zhang, Y., Hu, X., Liu, X., Dandan, Y., Di, D., Yin, T., Zhang, S., Tang, X., 2015b. Dry state microcrystals stabilized by an HPMC film to improve the bioavailability of andrographolide. Int. J. Pharm. 493, 214-223.

Zhang, Y.F., Li, Y.J., Yang, Q., Weng, X.G., Dong, Y., Zhu, X.X., 2010. Rat intestine absorption characteristics study on andrographolide with isolated everted intestine model Chin. J. Exp. Tradit. Med. Formulae 9, 34.

Zhao, X., Zu, Y., Li, Q., Wang, M., Zu, B., Zhang, X., Jiang, R., Zu, C., 2010. Preparation and characterization of camptothecin powder micronized by a supercritical antisolvent (SAS) process. J. Supercrit. Fluids 51, 412-419.

Zhu, Y.P., 1998. Chinese Materia Medica: Chemistry, Pharmacology and Applications. Harwood Academic Publishers, Amsterdam.

Zosel, K., 1981. Process for the decaffeination of coffee, in: Patent, U.S. (Ed.). Studiengesellschaft Kohle mbH, Kaiser-Wilhelm Platz, Fed. Rep. of Germany.

Zou, W., Xiao, Z., Wen, X., Luo, J., Chen, S., Cheng, Z., Xiang, D., Hu, J., He, J., 2016. The anti-inflammatory effect of *Andrographis paniculata* (Burm. f.) Nees on pelvic inflammatory disease in rats through down-regulation of the NF-κB pathway. BMC Complement. Altern. Med. 16, 483.

Zu, C., Zhao, X., Du, X., 2014. Enhanced water-solubility of Licorice extract microparticle prepared by antisolvent precipitation process. Adv. Powder Technol. 25, 787-794.