# *Hibiscus sabdariffa* Linn. (ROSELLE) EXTRACT NANOEMULSION FOR CONTROLLED-RELEASE CONSUMPTION AND ITS PHYSICOCHEMICAL PROPERTIES

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**ABSTRACT**

*Hibiscus sabdariffa* Linn. (Roselle) is well-known worldwide as a medicinal plant, which recently attracted the attention of scientists for its therapeutic characteristics. However, delivering the maximal anti-diabetic bioactive ingredients through the stomach lining is challenging. This is due to poor solubility and low bioavailability of bioactive substances. Therefore, a water-in-oil nanoemulsion was chosen as a carrier for the anthocyanidin glycosides' control-release (cyanidin-3-sambubioside, delphinidin-3-sambubioside, and delphinidin-3-glucoside-rich roselle extract. In this work, the nanoemulsion containing the roselle extract was prepared using a low-energy phase inversion- and high-energy technique using an ultrahomogenizer. Screening for suitable compositions of components of the W/O nanoemulsion containing the roselle extract, done by the ratio of surfactants Tween 80 to PGPR (11.2:15.7% – 13.3:17.8% w/w), the composition of canola oil:water (10%:58.7% - 10% :60.8% w/w), the effects of xanthan gum (0.1% - 0.3%w/w), and the concentration of roselle extract (0.1% -2% w/w). This work's ultimate goal is to formulate nanoemulsion containing concentrated roselle extract with minimum average droplet size (< 150 nm). The best compositions of the w/o nanoemulsion containing the roselle extract were Tween80: PGPR (12.5%:16.5% w/w), canola oil to water (10%:60.6% w/w), xanthan gum (0.2% w/w), and roselle extract (0.2% w/w) with a hydrophilic-lipophilic balance of 7.3. The transmission electron micrograph of the optimized w/o nanoemulsion containing the roselle extract exhibited the smallest particle size (133.6 nm) with a polydispersity index of 0.165. The optimized w/o nanoemulsion was an initial pH 3.4 with a low conductivity of 0.5 $\mu Scm^{-1}$, affirmed it is a w/o system. The nanoemulsion remained stable without any phase separation under an accelerated stability study (centrifugal force and freeze-thaw cycles) and temperatures 4, 25, or 40°C for up to 71 days of storage. In vitro release study at different pHs showed 0.17% (w/w) of the bioactive ingredients released at pH 6.8 (2 hours) compared to 0.12% (w/w) at pH 2.5 (2 hours) from the loaded 0.2% (w/w) drug amount at a maximal release of 3 hours. The release kinetics of w/o nanoemulsion containing the roselle extract showed linear relationships to all kinetic models for pH 6.8 and followed the first-order kinetic with the highest $R^2$ at 0.9986. Hence, the release of the w/o nanoemulsion containing the roselle extract followed the first-order kinetics at pH 6.8 under a simulated gut condition. Thus, the results conclude that the formulation exhibited possible application as a natural food supplement to treat diabetics.

# ABSTRAK

*Hibiscus sabdariffa* Linn. (Roselle) dikenali di seluruh dunia sebagai tumbuhan perubatan, yang baru-baru ini menarik perhatian para saintis kerana ciri-ciri terapeutiknya. Walau bagaimanapun, penghantaran maksimum bahan bioaktif anti-diabetes ini melalui lapisan perut adalah sukar. Ini disebabkan oleh keterlarutan dan bioketersediaan bahan bioaktif yang rendah. Oleh itu, nanoemulsi air-dalam-minyak (w/o) dipilih sebagai pembawa pelepasan-terkawal anthosianidin glikosida (sianidin-3- sambubiosida, delphinidin-3-sambubiosida), dan ekstrak roselle yang kaya dengan delphinidin-3-glukosida. Dalam kajian ini, nanoemulsi yang mengandungi ekstrak roselle disediakan dengan menggunakan teknik penyongsangan fasa tenaga rendah dan teknik tenaga tinggi menggunakan penghomogen ultra. Komposisi komponen nanoemulsi W/O mengandungi ekstrak roselle yang sesuai ditentukan melalui pemantauan nisbah surfaktan Tween 80 kepada poligliserol poliricinoleat (PGPR) (11.2: 15.7% −13.3:17.8% w/w), komposisi minyak canola:air (10%: 58.7% − 10%: 60.8% w/w), kesan gam xanthan (0.1% − 0.3% w/w), dan kepekatan ekstrak roselle (0.1−2% w/w). Tujuan utama kajian ini adalah untuk menghasilkan nanoemulsi yang mengandungi ekstrak roselle pekat dengan ukuran titisan purata minimum (<150nm). Komposisi terbaik nanoemulsi W/O yang mengandungi ekstrak roselle ialah Tween 80:PGPR (12.5%: 16.5% w / w), minyak canola:air (10%: 60.6% w/w), xanthan gum (0.2% w/w) ), dan ekstrak roselle (0.2% b/b) dengan keseimbangan hidrofilik-lipofilik pada 7.3. Mikrograf elektron transmisi nanoemulsi W/O yang mengandungi ekstrak roselle teroptimum menunjukkan ukuran zarah titisan terkecil (133.6 nm) dengan indeks polidispersiti sebanyak 0.165. Nanoemulsi W/O teroptimum berada pada pH 3.4 dengan kekonduksian rendah sebanyak 0.5 $\mu Scm^{-1}$, membuktikan ianya adalah suatu sistem W/O. Nanoemulsi ini tetap stabil tanpa pemisahan fasa di bawah kajian kestabilan dipercepat (daya sentrifugal dan kitaran pembekuan-pencairan) dan pada suhu 4, 25, atau 40 °C hingga 71 hari penyimpanan. Kajian pelepasan in vitro pada pH yang berbeza menunjukkan 0.17% (w/w) bahan bioaktif telah dilepaskan pada pH 6.8 (2 jam) berbanding 0.12% (w/w) pada pH 2.5 (2 jam) dari sejumlah 0.2% (w/w) ubat yang dimuatkan pada pelepasan maksimum selama 3 jam. Kinetik pelepasan nanoemulsi W/O mengantuk ekstrak roselle menunjukkan hubungan linear dengan semua model kinetik pada pH 6.8 dan mengikuti kadar pertama kinetik dengan $R^2$ tertinggi pada 0.9986. Oleh itu, pelepasan nanoemulsi W/O mengandungi ekstrak roselle telah mematuhi kadar pertama kinetik pada pH 6.8 di bawah simulasi keadaan perut. Hasil dapatan kajian ini dapat dirumuskan bahawa formulasi ini berpotensi untuk digunakan sebagai makanan tambahan semula jadi untuk merawat pesakit diabetes.

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## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| DM | - | Diabetes Mellitus |
| T1DM | - | Type1 Diabetes Mellitus |
| T2DM | - | Type2 Diabetes Mellitus |
| GDM | - | Gestational Diabetes Mellitus |
| DS | - | Dietary supplement |
| HS | - | *Hibiscus sabdariffa* |
| O/W | - | Oil in water |
| W/O | - | Water in oil |
| TEM | - | Transmission Electron Microscope |
| IR | - | Insulin resistance |
| HLB | - | Hydrophile-Lipophile Balance |
| DHA | - | Edible Docosahexaenoic Acid |
| EPA | - | Eicosapentaenoic Acid |
| PDI | - | Polydispersity index |
| DLS | - | Dynamic light scatter |
| AFM | - | Atomic force microscopy |
| DI | - | Deionized water |
| PGPR | - | Polyglycerol Polyricinoleate |
| TEM | - | Transmission Electron Microscopy |
| PBS | - | Phosphate Buffer Saline |
| OSA | - | octenylsuccinc anhydride |
| XG | - | Xantham gum |

# LIST OF SYMBOLS

| | | |
|---|---|---|
| $\Delta G$ | - | Gibbs free energy |
| $\Delta A$ | - | Surface area |
| $\gamma$ | - | Interfacial tension |
| $\Delta S$ | - | Entropy |
| RH | - | Hydrodynamic radius |
| KB | - | Boltzmann constant |
| T | - | Temperature |
| $\eta$ | - | Viscosity |
| D | - | Diffusion coefficient |
| r | - | mean radius after time |
| $r_o$ | - | the value at a certain time |
| t | - | frequency of rupture per unit of the dialysis bag surface |
| $\omega$ | - | the frequency of rupture per unit surface of the dialysis bag |
| $C(\infty)$ | - | bulk phase solubility |
| $V_m$ | - | molar volume of the internal phase |
| $D$ | - | diffusion coefficient of the dispersed phase in the continuous phase |
| µg | - | Microgram |
| ml | - | Millilitre |
| min | - | Minute |
| nm | - | Nanometer |
| rpm | - | Rotation per minutes |
| µL | - | microliter |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of Research

Diabetes mellitus is a severe and long-term disease that has a profound impact on the lives and well-being of population around the world (Saeedi *et al.*, 2019). It is blamed for the deaths of millions per year. Diabetes rate is expected to rise globally from 415 million in 2015 to 642 million in 2040 (Gupta *et al.*, 2016). A recent report indicated that nearly fifty percentage of the people living with diabetes were not given a diagnosis (Obafemi *et al.*, 2019). There are three common types of diabetes, type 1 diabetes mellitus (T1DM), type II diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (Saeedi *et al.*, 2019). Increased blood glucose, carbohydrates, and lipid levels are common for diabetes (Shadhan and Bohari, 2017). Type II diabetes mellitus (T2DM) or non-insulin-dependent diabetes has to be the most widely recognized type of diabetes, responsible for around 95% of cases (Bule *et al.*, 2020).

Diabetes mellitus is defind as a chronic disease that happens when the body cannot use the insulin generated properly or when the pancreas does not contain enough insulin. Insulin is an major  hormone that controls sugar levels (Shadhan and Bohari, 2017). It will be important to note that insulin resistance is the major contributing cause of type 2 DM. The drop in insulin in the blood stimulates glucose dysmetabolism in multiple tissues. Such unwanted metabolism changes are the biggest factor for human hyperglycemia and diabetes (Shadhan and Bohari, 2017). Although some different medication methods for diabetes have become usable, therapies are also slightly unfavourable. Concerns having to do with the use of medications and their adverse effects on people with diabetes. This has prompted some people to pursue natural treatments, such as conventional herbal remedies (Kamel *et al.*, 2017).

Herbal remedies have been accepted as substitutes and complementary medicines since previous centuries (Alkhamaiseh and Aljofan, 2020). Herbs have long been recognised as potentially beneficial therapies for diabetes and are increasingly being used by people today (Kamel *et al.*, 2017). Over the last few years, the accentuation on plant science has grown massively to investigate the vast properties of plants used in various conventional methods. laboratory studies on plants' pharmacological properties revealed an array of powerful phytochemical agents to treat different kinds of diseases. Among the studied plants is the *Hibiscus sabdariffa* Linn. (Riaz and Chopra, 2018).

Karkade and roselle are the other names of *Hibiscus sabdariffa* Linn., belonging to the Malvaceae group (Shadhan and Bohari, 2017). Each part of the roselle plant has well-reported medicinal purposes and is explored as different foods. An appreciable number of medicinal properties of roselle was described. These included hepatoprotective, antihypertensive, renal/diuretic, anti-oxidative, hypolipidemic, anti-cholesterol, anti-cancer, and anti-diabetic properties (Zannou *et al.*, 2020). Pertinently, the roselle flower extract is rich in anti-diabetic agents comprising of delphinidin-3-sambubioside, cyanidin-3 sambubioside, and delphinidin-3-glucoside. These substances are proven potent in controlling blood sugar (Cid-ortega et al., 2015). The plant is popular in certain regions of the world for treating anemia, relieve fever, wound healing, colds, measles, cough, dizziness, and conjunctivitis. The fresh or dried calyces of roselle are appreciated and taken as cold or hot herbal drinks. The more innovative way to enjoy roselle is their transformation into jellies, fermented drinks, chocolates, wine, ice cream, juices, tea, jams, and syrup (Zannou *et al.*, 2020).

Food dietary supplements (DS) are essential for improving and maintaining human energy and wellness; thus their properties are close to those of pharmaceutical drugs (capsules, dragees, and tablets) (Dlugaszewska *et al.*, 2019). however, medicinal uses for bioactive herbal extracts are constrained by the low solubility, bioavailability, and permeability. The same issue also exists when attempting delivery of adequate doses of the bioactive substance-rich roselle extracts. This is because the human body tends to rid off the bioactive compounds if administered in high doses, akin to the fate of water-soluble vitamin C that becomes excreted as highly nutritious urine (Chambial and Dwivedi, 2013). These aforesaid issues remain challenging to the effective use of high doses of herbal bioactive compounds to treat various health problems. In this milieu, nanoemulsion technology can resolve the abovementioned shortcomings (Harwansh *et al.*, 2019) by integrating bioactive plant extracts as nano-droplets in food suspensions (Kheynoor *et al.*, 2018). The nanosize droplets could produce a steady release of the bioactive components and improve their bioavailability (Harwansh *et al.*, 2019). Nanoemulsions are unique colloidal delivery mechanisms that conserve, encapsulate, and carry lipophilic bioactive compounds. The droplet sizes typically range between 20 - 200 nm. Nanotechnology has been around for a decade and is gaining popularity in the food processing and pharmaceutical sectors (Marwaha and Dabas, 2019), particularly to improve the delivery of sensitive hydrophilic materials (Kheynoor *et al.*, 2018).

## 1.2 Problem Statement

While most available anti-diabetic medications are successfully maintaining stable blood glucose rates, their administration has resulted in note-worthy side-effects (Sheikh, 2016). Though extracts from calyces of roselle flowers are rich in relatively water-soluble anti-diabetic agents delphinidin-3-sambubioside, cyanidin-3 sambubioside, and delphinidin-3-glucoside-rich are thought to be promising diabetes treatment options (Kamel *et al.*, 2017), the treatment efficacy through oral delivery may be hampered. The human body's natural proclivity excretes high doses of water-soluble bioactive compounds through urine. This is due to the body's inability to absorb the compounds through the gut lining within a short duration (Rein *et al.*, 2012). Hence, a more targeted and sustained oral delivery system for the roselle extract supplement is needed to meet the nutritional need of diabetic patients.

This study proposed the formulation of a W/O nanoemulsion containing the anti-diabetic agents from roselle flowers extract for oral consumption. This formulation could sustain a steady release of the ingredients for better absorption through the gut lining within 4-6 hours of consumption. The study aimed to overcome the rapid excretion of the water-soluble anti-diabetic active ingredients when administered by oral delivery. Also, the kidney operation is not overburdened by the need to flush out high concentrations of active ingredients. To do so, the study must identify the best composition and mixing protocol for a stable W/O nanoemulsion containing the roselle extract.

Furthermore, nanotechnology is a proven promising method for delivering bioactive herbal extracts to target sites on the body. The benefits come from the micelles of delphinidin-3-sambubioside, cyanidin-3 sambubioside, and delphinidin-3-glucoside that produce their sustained release profile. The reduced droplet size also promotes their bioavailability (Alexander *et al.*, 2016) to diabetic individuals. This, in turn, helps to regulate their blood sugar levels. The W/O nanoemulsion containing roselle extract can result in a controlled release of the anti-diabetic agents during digestion and permit more sustained absorption (Cid-ortega et al., 2015). Noteworthily, this study details the first attempt to develop a nano emulsified food supplement containing anti-diabetic ingredients from the extract of roselle calyces.

## 1.3 Objectives of the Study

This study aims to prepare an anti-diabetic nanoemulsion containing concentrated roselle extract. To achieve this, the objectives of the study are to:

i. To formulate a kinetically stable W/O nanoemulsion containing concentrated roselle extract.
ii. To characterize the physicochemical characteristics of the W/O nanoemulsion containing the roselle extract.
iii. To carry out an in-vitro control release study of the W/O nanoemulsion containing the roselle extract.

## 1.4 Scopes of the Study

In this study, the delphinidin-3-sambubioside, cyanidin-3 sambubioside, and delphinidin-3-glucose in the roselle's dry powder flowers were extracted by stirring the roselle powder in ultra-pure water. The suspension was then filtered and directly used to prepare the aqueous phase of the W/O nanoemulsion for oral delivery. The composition comprised appropriate amounts of Polysorbate 80 (Tween 80) and Polyglycerol polyricinoleate product type 4150 (PGPR) as non-ionic surfactants to stabilize the formulation. The study carried out composition screening on the W/O nanoemulsion containing the roselle flower extract, for parameters surfactants, oil, xanthan gum, bioactive extract, and water, to give the smallest particle size and the lowest polydispersity index (PDI). The components were mixed by a temperature inversion method. This was followed by a high energy method using an ultrahomogenizer to obtain a complete W/O nanoemulsion.

The physicochemical characteristics of the stable W/O nanoemulsion containing the roselle extract were characterized by Transmission Electron Microscope (TEM), particle size, and zeta potential to establish its morphology. Next, stability studies were done by subjecting to three tests: i) centrifugation, ii) storage stability against particle size at different storage temperatures, and iii) freeze-thaw cycles. Long-term monitoring for pH and particle size changes were also done. Lastly, viscosity- and conductivity tests were also done.

The controlled-release profile study of the roselle extract W/O nanoemulsion was done using a dialysis bag made of cellulose acetate membrane with a cut-off point of 1000 kDa. The release profile was monitored over 3 h, and the components were detected by UV-Vis spectrophotometer assay. In this investigation, the highest amount of roselle release from the W/O nanoemulsion and establishes the completion time that released all the components.

## 1.5 Significance of the Study

The outcome of this study establishes the formulation protocol to prepare a kinetically-stable W/O nanoemulsion containing concentrated roselle extract as a food supplement to control blood sugar in people with diabetes. The optimized formulation could yield a more sustained release of the anti-diabetic active ingredients and improve their bioavailability to diabetic individuals.

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