ABSTRACT

Herbal medicine is one of the rising trends in modern times, used to not only provide supplements but in times also to provide prevention of deadly diseases. One of the uses of herbal medicine is celery to treat hypertension, the "silent killer" and the cause of the highest mortality rate in the world. However, there are few studies on using celery herb extract as an antihypertensive agent. Additionally, the difference in extraction method may cause a difference in the extract characteristics, resulting in formulation difference. Therefore, this research aims to find the most optimum excipient provided by the research area to use in the celery herb extract capsule. This study used a pure experimental method using celery herb extracts formulated in capsule dosage forms. The excipients used in this research are Silicon dioxide, Microcrystalline Cellulose 102, Starch, Talcum, and Magnesium Stearate.

Eight formulas were constructed for this study, with each of them varying between the amount of each excipient and the type of filler being put into each Formula. Each Formula was assessed differently based on the step that the research was on. Generally, the formulas were assessed based on their organoleptic, moisture content, granule flowability, tapped density, disintegration testing, active ingredients testing, and microbial testing excluding aflatoxin and heavy metals testing. These tests were referred to Indonesia's National Agency for Food and Drugs Control law number 32 of the year 2019 about the Requirements for Safety and Quality of Traditional Medicine. The result of each test was then compared to the set requirement, and the Formula chosen for pilot testing was based on the requirement.

The Formula chosen for pilot testing was composed of the following excipients: 10% Silicon Dioxide, 80% of Microcrystalline Cellulose 102, 7% Amylum, 2% talcum, and 1% Magnesium Stearate. The Formula was assessed using the previous requirements for every step and has been found to have passed every requirement by Indonesia's National Agency for Food and Drugs Control and Internal Company Regulations, which suggested the Formula is composed of the most optimum excipient.

Keywords: Herbal medicine, Celery Herb capsule, Anti-Hypertension

CHAPTER I
INTRODUCTION

A. Background

Being a tropical country in Southeast Asia, Indonesia has been known to have a vast amount of native plants within its vicinity. It is predicted that around 25,000 – 30,000 plants in Indonesia can be made into herbal medicine, and about 1,845 identified plants could be used as medicine. Sadly, according to Susidarti (2017) in the journal "*Tanaman sebagai sumber senyawa bioaktif: peranannya dalam terapi dan pengembangan obat baru,*" the full potential of Indonesia's herbal plants has not been unlocked since only about 200 species of 30,000 species have been used for medicinal purposes.

Herbal medicine is a type of supplement sold in many types of forms. However, unlike conventional medicine, whose active ingredients are made in a laboratory, herbal medicine's active ingredients are taken from plant parts, such as leaves, stems, roots, flowers, and even seeds.

According to the World Health Organization, hypertension is also commonly known as the "silent killer" as it is easy enough to kill people without symptoms. Additionally, it can also cause complications that can lead to stroke and heart diseases which claim about 16% of deaths globally, and celery might be one of the key factors to turn the statistics around. Additionally, it can also cause chest pain or angina and tachycardia, which can lead to sudden death.

Celery is one of the most common vegetables we can search for these days. Although stem leaves and seeds can all be used as medical treatment, not many people know of their various medicinal properties. One of the benefits of using celery as herbal medicine is its anti-hypertensive effects.

Despite that, one of the disadvantages of herbal medicine is its taste and odor. Thus, industries tend to find other ways to negate that negative effect, such as making it into a capsule, tablet or even formulating it to be a sweet concoction to consume.

Vegetable capsules were also chosen as a shell for the granules within this research. This is because vegetable capsules are strictly made out of plants, specifically the hydroxypropyl methylcellulose part, which is easier for Indonesians to accept due to their culture. This is why vegetable capsules are a better alternative to gelatin and why we chose to use vegetable capsules as a substitute.

Despite its many benefits, the characteristic of a celery extract may vary depending on the method used to extract, including the temperature and time of extract and the solvent used to extract the celery. This is why optimization of the excipients is needed to ensure the granule is up to the current standard.

B. Problem Statement

1. Which celery extract granule formulation meets the requirements for a good capsule?
2. How are the characteristics of celery extract capsules from the chosen formulation?

C. Study Urgency

Extract formulation is one crucial step in producing high-quality herbal medicinal products. However, herbal extracts may vary in physicochemical properties, which need further studies to find the most optimum formulation for a particular dosage form. The capsule is one of the favorite dosage forms available for herbal extract. In addition, there might need to be some adjustments when making granules on a pilot scale. Therefore, it is crucial to research to develop a new formulation to counter this challenge.

D. Study Objectives

This study aims to find the best excipient out of the ones provided used in the celery capsule formulation which will be tested based on the requirements set by Indonesia's National Agency of Drug and Food Control.

E. Literature Review

1. Herbal Medicine

Herbal medicine is a type of alternative medicine used to prevent or even help lower symptoms of certain diseases as a supplement (Firenzuoli & Gori, 2007). It is taken from herbs, native plants growing within a country, or even from foreign plants and their respective active ingredients. Therefore, it could be said that herbal medicines are finished products within containers that have a pharmacologically effective plant for treatment inside it (Glynn & Bhikha, 2018). However, with the ever-changing environment that each country offers, it is impossible to pinpoint a certain standard for every plant's chemical marker.

Additionally, its effect may vary from person to person depending on various variables (Firenzuoli & Gori, 2007).

It is also worth noting that even though it may be “natural,” it may not be particularly effective in low dosage or even be safe to consume in high dosage. However, the public is usually misguided into thinking that every natural medication is safe to consume when it carries side effects (Phua et al., 2009). Thus, the common question that has not been thoroughly answered is that consuming herbal medicine might also cause it to interact with other medications that people have been consuming and give people side effects when people are allergic to it. So, even though the usage of herbal medicine dates back thousands of years ago, their effectiveness and safety remain controversial to this day.

Regardless of that, there are many reasons that people would choose to consume herbal medication rather than the conventional one. According to a study done by Welz et al. (2018) in Germany, patients would usually use herbal medicine as a starting treatment before using conventional medicine. Although, according to the same study, consuming herbal medication without an expert’s opinion and self-awareness may be potentially harmful towards the user if unidentified incorrectly. Nonetheless, medicinal plants are said to have fewer side effects than conventional drugs; this is also one of the main reasons people would occasionally choose herbal medicine rather than conventional ones (Sutiswa & Rahman, 2020).

It is also worth mentioning that even though herbal medicines have a lower efficacy compared to conventional ones, they may also pose a threat to the user should someone consume them together. This is because there are tons of unidentified active ingredients within herbal medicine that may pose a synergistic effect or an antagonistic effect towards the user if they were to consume it with conventional medicine. Therefore, it is crucial to analyze which herbal medicine interferes with conventional medicine before use (Glynn & Bhikha, 2018).

2. Celery

a. Celery Classification

According to a book written by Fazal and Singla (2012), celery can be classified as:

Kingdom : *Plantae*

Division : *Spermatophytes*

Sub-division : *Angiospermae*

Class : *Mangnolisisa*

Sub-class : *Rosidace*

Ordo : *Apiceae*

Family : *Apiceae*

Genus : *Apium*

Species : *gravolens*

b. Celery Morphology

Figure 1. Celery (Apium graveolens) (Kooti et al., 2016)

Celery (*Apium graveolens*) is part of the *Apiaceae* family and one of the annual plants that grow throughout Europe and Africa, and the subtropical parts of Asia. It grows on average up to 1 meter and has broad, solid branches and stems. It has a non-woody stem, which is segmented and has a pale green color (Majidah et al., 2014). Its leaves have a unique shape of rhombus or oval with a jagged side, a rough surface on either side, a lighter color on the backside than the upper side. On average, its leaves have a length of about 2 - 7.5 cm and a width of 2 - 5 cm (Majidah et al., 2014). It also has an aromatic fragrance. While it may not taste like much the first couple of seconds, it will slowly taste spicy (Depkes RI, 2017).

According to a pharmacological analysis, almost every part of celery is valuable as medicine. The plant's roots can be used as a diuretic. The seeds and fruits can be used as antispasmodic, reducing the uric acid in the blood and antirheumatic. Celery is also used as a sedative, carminative, anti-inflammation, antioxidant, antibacterial, anti-cancer, and antihypertensive agent (Dewi et al., 2016; Syahidah & Sulistyaningsih, 2018). Celery could also be used to treat gout, headache, anorexia, and tiredness.

1. Celery Herb Components

An NMR examination of celery blade leaves revealed the presence of amino acids such as alanine, asparagine, aspartate, -aminobutyrate, glutamate, leucine, lysine, isoleucine, proline, threonine, and valine, according to a paper published by Ingallina et al. (2019). Within the leaves, malic, citric, acetic, succinic, lactic, pimelic, and quinic acids were discovered. Mannitol, the major polyol found in celery, was also shown to dominate the 3.6-3.9 ppm range. In addition, various polyols (Myo-inositol and scylloinositol), carbohydrates (α and β-glucose, sucrose, β-δ-fructopyranose, β-δ-fructofuranose, β-δ-fructofuranose), choline, and ascorbic acid were also detected in other ranges. In addition, indications of amino acid aromatic groups (phenylalanine, tryptophan, and tyrosine), as well as formic, fumaric, shikimic, and caffeoylquinic acids, were found in the low-frequency spectrum region. In the case of petioles, glutamine signals were also discovered, but lysine and caffeoylquinic acid signals were not (Ingallina et al., 2019).

a. *Flavonoid*

Flavonoids are a class of bioactive polyphenolic chemicals found in a wide range of plants and herbs. They have cardio-vasculoprotective properties and may help prevent the beginning or progression of several cardiovascular disorders, including hypertension. Catechins and quercetin have been shown to reduce blood pressure in human randomized controlled trials (RCTs).

Flavonoids work to lower blood pressure via boosting nitric oxide (NO) bioavailability, decreasing endothelial cell oxidative stress, and modifying vascular ion channel function (Maaliki et al., 2019).

b. *Apigenin*

Apigenin, also known as 4′, 5, 7-trihydroxyfavone, is a flavonoid molecule with anti-inflammatory and antioxidant properties. The initiation and course of hypertension and hypertension-induced cardiac hypertrophy are influenced by chronic, low-grade inflammation and oxidative stress. Apigenin may decrease hypertension by modulating NADPH oxidase-dependent ROS production and inflammation in the PVN of spontaneously hypertensive rats (Gao et al., 2021).

c. Celery as an Antihypertensive

Another benefit that comes from the use of celery is its anti-hypertensive effect. A study conducted by Moghadam et al. (2013), showed that the extract of celery seed lowered the blood pressure of the hypertensive rats that they experimented on but had no effects on the normotensive rats.

It was found that one of the flavonoids in celery, called apigenin, lowers the contractility of smooth muscles in the heart, thus creating a vasodilator effect (Je et al., 2014; Naqiyya, 2020). The contraction mechanism happens when there is an increase in calcium within the cell, causing the calcium in the cytosol to increase and triggering the contraction of blood vessels, thereby increasing the blood pressure. Suppose it occurs in the cardiac muscle cells. In that case, it will strengthen the muscle heart's contraction so that the heart pumps harder and increases blood pressure (Anggraini et al., 2016). The apigenin in celery blocks the calcium channel, which is responsible for increasing the heart's contraction, hence decreasing the heart's contraction, dilating the arteries so that the blood flows smoothly, and decreasing the blood pressure (Naqjyya, 2020).

Vitamin C helps maintain normal blood pressure by preventing cholesterol build-up in the arterial walls. Vitamin C will also increase the rate at which cholesterol is removed and increase HDL levels so that it will restore the elasticity of blood vessels (Arie et al., 2016; Oktadoni & Fitria, 2016).

The potassium in celery is known to decrease the extracellular fluid volume by pulling it into the intracellular fluid, resulting in a change in the balance of the sodium-potassium pump, which will cause a decrease in blood pressure. One of the strategies used in managing hypertension is to change the balance of sodium levels (Oktadoni & Fitria, 2016).

Celery also contains phytosterol, a phytochemistry component that is useful to combat cholesterol. Phytosterol in the celery is used to prevent arteriosclerosis, a complication caused by endothelial dysfunction due to hypertension (Dwinanda et al., 2019). Magnesium and iron substances in celery can clean the rest of the metabolism and excess fat deposits in the blood vessels, thus preventing stiffness in the blood vessels without vascular retention (Oktadoni & Fitria, 2016).

Apart from that, celery also contained 3-n-butyl phthalide (3nB), one of the components responsible for a celery's unique smell and was also found to contribute to lowering high blood pressure relaxing the smooth muscles of the blood vessels (Oktadoni & Fitria, 2016). Administration of 300 mg/kg for each ethanol, methanol and hexane extract of celery seeds can lower blood pressure by 23, 24, and 38 mmHg and increase heart rates by 27, 25, and 60 beats per minute. Analysis results with high-performance liquid chromatography (HPLC) show that the content of n-butylphthalide (NBP) in celery hexane extract is 3.7 - 4 times greater than the methanol and ethanol extracts. The NBP compound in celery has become an active hydrophobic constituent as an antihypertensive (Moghadam et al., 2013).

2. Capsule Formulation

a. Filler

Diluents are fillers used to make a tablet or capsule's bulk volume larger. The end product is given suitable weight and bulk to aid production and handling by combining a diluent with the active medicinal components. A diluent should be unreactive so that it does not cause therapeutic properties of its own, it should also be compatible with the active substance and other excipients used in the formulation, it should be non-hygroscopic so that the formulation does not absorb significant amounts of water from its surroundings, it should be compatible and of similar particle size to the active ingredient to provide satisfactory performance in a capsule dosage form (Hartesi et al., 2016)

1. *Microcrystalline Cellulose*

Microcrystalline cellulose is a pure, partially depolymerized cellulose that comes in a white, odorless, and tasteless crystalline powder with porous particles. Microcrystalline cellulose is a frequently utilized binder or diluent in oral tablet and capsule formulations. It is used in both wet-granulation and direct-compression methods (Rowe et al., 2009)

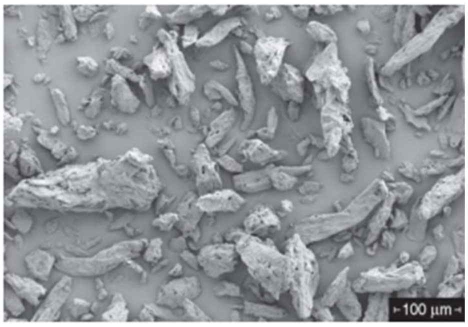

Figure 2. Microcrystalline Cellulose 102 (Rowe et al., 2009)

2. *Amylum Manihot*

Amylum *Manihot* is a fine white powder with no odor, no taste, is non-toxic, and irritates the skin. Starch comprises two polysaccharides based on a-(D)-glucose: linear amylose and branching amylopectin (Rowe et al., 2009)

Starch is used as a filler in creating standardized triturates of colorants or potent pharmaceuticals to aid mixing and blending procedures in manufacturing operations. For volume modification of the fill matrix, starch is also employed in dry-filled capsule formulations (Hartesi et al., 2016).

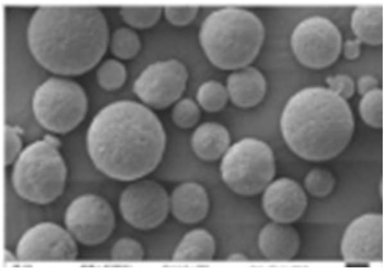

Figure 3. *Manihot* Starch (Xia et al., 2017)

3. *Anhydrous Lactose*

Anhydrous lactose is commonly utilized as a tablet and capsule filler and binder in direct compression tableting applications. In addition, because of its low moisture content, anhydrous lactose can be utilized with moisture-sensitive medicines. Lactose anhydrous comes in white to off-white crystalline particles or powder form. Several brands of anhydrous lactose on the market contain both anhydrous b-lactose and anhydrous a-lactose. 70–80 percent anhydrous b-lactose and 20–30 percent anhydrous a-lactose are found in anhydrous lactose (Rowe et al., 2009).

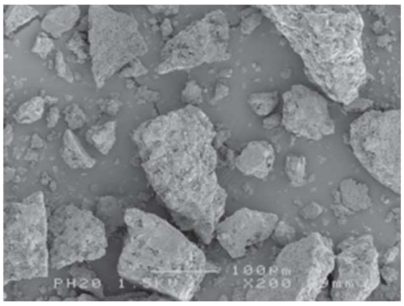

Figure 4. Anhydrous Lactose (Rowe et al., 2009)

b. Drying Agent

The function of a drying agent is to remove traces of water to produce a dryer granule. This will in turn help out the granulation process for sticky and hygroscopic extracts.

1. *Silicon dioxide*

Pharmaceuticals, cosmetics, and food products all use colloidal silicon dioxide. Its small particle size and wide specific surface area provide it with ideal flow qualities, which are used to improve the flow properties of dry powders in a variety of procedures like tableting and capsule filling (Rowe et al., 2009).

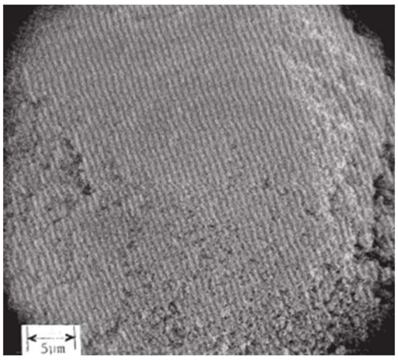

Figure 5. Silicon dioxide (Rowe et al., 2009)