A Systematic Review of Ume Health Benefits

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May 18, 2016
Abstract

Ume is a Japanese apricot, and Bainiku Ekisu (BE) is concentrated ume juice. Ume has been used as a food and folk remedy for thousands of years in East Asian countries, and BE was created in Japan centuries ago and has been used as a remedy since. In the Western world, the nutritional and medicinal benefits of ume and BE are not popularly known, despite many experimental studies showing their numerous health benefits. There are no known systematic reviews of the health benefits of ume and BE. Therefore, this systematic review describes the last 20 years of quality empirical studies that investigate ume and BE health benefits. It finds 27 quality studies that confirm ume and BE’s more than 20 benefits, including anti-cancer, anti-inflammatory, anti-oxidative, anti-microbial, and anti-viral effects when observed in both laboratory tests and clinical studies. Therefore, individuals, conventional and holistic health professionals should consider ume and BE for their nutritional and medicinal properties.
Acknowledgements

The author would like to acknowledge the support of the learning center in Minneapolis campus, Debra Evon, Perry Lueders, Anna Altman, and Emily Muelken, the librarian, Sue Grey, instructors, Carol Geisler, Janet Dahlem, Stasia Johnson Steinhagen, classmates, and my friend, Jennifer Anton Bakken.
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Introduction

Ume, whose scientific name is *Prunus mume* Sieb. et Zucc., is a valuable source of food and medicine in Japan, Korea and China due to its nutritional, therapeutic benefits as well as its aroma and flavor (Yu et al., 2015). It has been told by many generations in Japan that “ume cleanses three poisons” which are food poison, blood poison and water poison (Matsumoto 2000, p. 72). In one story, my father was unable to move an inch due to suffering from mountain altitude sickness and extreme fatigue when he was climbing Mt. Fuji. Fortunately, his friend brought salted pickled ume fruit (umeboshi) and he ate one. Immediately after eating umeboshi, his body was revitalized, and he was able to climb to the top of the mountain (K. Miyazaki, personal communication, January 4, 2000). This story demonstrates that umeboshi has a powerful effect of boosting one’s energy. According to Okubo (2013), the effects of umeboshi are killing bacteria and cleansing one’s blood. These effects induce revitalization and recovery from fatigue.

However, as Rosenthal (2011) argues umeboshi contains too much salt that could cause high blood pressure or stomach cancer. Solving this high content of salt issue, Matsumoto (2000) states that concentrated juice of ume fruit called bainiku ekisu (BE), which is another folk remedy in Japan, is a healthy and effective way to prevent diseases including cancer, heart disease, intestinal disease, osteoporosis, liver diseases and liver inflammation; BE also improves blood fluidity, enhances the immune system and offers many more health benefits without any side effects. In addition to this, Fujimaki (2005) states that BE prevents kidney disease, neuralgia, hormonal imbalance and poor circulation. Moreover, salt is not added to this concentrated juice at all, which makes it healthier than umeboshi. Therefore, BE has been a
treasure for millennia in Japan; these findings suggest that ume, in the form of BE, may be a “super medicine.”

According to Matsumoto (1998), the process of producing BE is time consuming, and only about 20g (0.7 oz.) is produced from 1kg (2.2 lbs.) of fresh green-unripened ume. Even though production is limited, Fujimaki (2005) notes that people only need to take a tiny portion of BE daily to maintain their optimal health. More precisely, Matsumoto (2000) states that taking 3 grams (0.1 oz.) a day of BE is the right amount for a person who weighs 55kg (121 lbs.). Also, BE has long been thought to have a powerful sterilizing property which prevents intestinal disorders. Therefore, it has been traditionally used as a specific medicine for food poisoning, diarrhea, constipation and colds. In addition to BE, alcohol soaked ume, fermented ume and green tea with ume, have been used as foods as well as medicine for centuries in Japan and other Asian countries. Wu et al. (2011) report that the raw ume fruit is poisonous because it contains two types of cyanogenic glucosides, prunasin and amygdalin. Therefore, since ancient times, ume had been processed in many different ways as food and medicine.

Recently, modern science discovered numerous health benefits from processed ume, including specific compounds and constituents such as mumefural, MK615, phenols, organic acids and many more (Hoshino et al., 2013; Matsumoto, 2000; Nakagawa et al., 2007; Tada et al., 2011; Wu et al., 2011). These compounds and constituents play an important role in preventing and treating numerous diseases. Ancient knowledge has been slowly justified by recent research and my hope is to make this ancient knowledge more accessible to the general public so that many people with and without health issues can benefit from this natural medicine. Although many health benefits have been discovered by recent research, ume is not well known in Western countries. In addition, systematic review of literature has not been conducted in ume
research. Therefore, the purpose of this research is to describe the health benefits of ume and BE by using systematic review of literature.

This research project begins in chapter two with a review of the literature covering the history of ume, recent discoveries of health benefits in BE, and recent discoveries of health benefits in ume using different processes and extraction methods. After the literature review, lenses chapter offers my theoretical, personal, and professional lenses that discuss my current beliefs and the perspectives that have influenced this project. Following this chapter, the method chapter provides details about the research project. Next chapter includes the major results of this study. Finally, discussion chapter contains findings, implications and conclusion.
A SYSTEMATIC REVIEW OF UME HEALTH BENEFITS

Literature Review

The purpose of this chapter is to review and examine the literature related to ume (Prunus mume Sieb. et Zucc), to convey how precious ume was for ancient people, and to explore recent pharmacological and biomedical discoveries about ume that impact one’s health. In order to explore these facts, this chapter begins with the history of ume including history of ume as a remedy in East Asia, and ume as a remedy and food in Japan. Next, the chapter includes recent discoveries of health benefits in BE, and recent discoveries of health benefits of ume using different processing techniques.

History of Ume

This section is divided into two categories. The first concerns the history of ume as a remedy in East Asia, and the next covers ume as a remedy and food in Japan.

History of ume as a remedy in East Asia. The ume plant has a long history of being part of ancient people’s lives. Ume or Prunus mume Sieb. et Zucc, belongs to the Rosaceae family (Mitani et al. 2013) and has been grown in Japan for more than 2000 years (Yamashita et al., 2012). Chuda et al. (1999) note that now there are 400 varieties worldwide. According to Matsumoto (1998), ume originally came from China, and an archaeological discovery in 1979 indicated that people had been consuming ume for more than 7000 years. Moreover, Matsumoto (2000) notes that ancient Chinese people already identified the benefits of ume as a remedy about 2000 years ago. One of the proofs is that benefits of ume were written about 2000 years ago in Shinnouhonsoukyo, which is the oldest textbook of traditional Chinese medicine. In Shinnouhonsoukyo, an anonymous author (as cited in Matsumoto, 2000) states that ubai, which is smoked ume, can be used as an astringent. Ubai is used to treat the lungs, improve intestinal activation, reduce fever, enhance stomach activity and kill bacteria in the body. Ubai was first
introduced to Japan about 2000 years ago from China (Matsumoto, 2000). Kampo medicine (herbal medicine) based on traditional Chinese medicine was introduced to Japan along with ubai and it was widely practiced (Yamanouchi & Yamagami 1987).

Jung, Cho, Koh, Han and Lee (2010) report that the flower, branch, leaf, seed and root of the ume plant have all been used as medicine in Asian countries. Korean people also discovered the benefits of ume. Traditionally in Korea, unripened fruit was processed as a remedy for dyspepsia, cough and skin disorders (Jung, et al, 2010a). Kishima (1999) reports that ume was not only used for practical reasons, but it also fascinated people with beautiful flowers in spring. People can enjoy beautiful red, pink and white ume flowers found everywhere in the early spring time in Japan and other Eastern Asian countries.

**Ume as a remedy and food in Japan.** Since the time ume was introduced to Japan from China, ume has played an important role in the Japanese people’s lives. Yamashita et al. (2012) note that people discovered the health enhancing effects of ume soon after it was introduced to Japan, and they have improved the species of ume tree to produce healthier fruits. As mentioned previously, according to Terada and Sakabe (1988) and Ohtsubo and Ikeda (1994), one drawback is that raw ume fruit is poisonous due to two types of cyanogenic glucosides, which are amygdalin and prunasin. In Japan, it is common knowledge that people should never eat green raw ume. Consequently, Chuda et al. (1999) note that it is necessary to process ume by pickling in liquor, fermenting, heating and concentrating it into syrup or concentrated fruit juice.

Yamashita et al. (2012) state that traditionally Japanese ume juice was considered to suppress cancer and inhibit bacterial growth. According to Wu et al. (2011), “P. mume contains many basic nutrients, including proteins, carbohydrates, dietary fiber and multiple vitamins” (p.66). In addition to this, organic acids, such as malic acid, succinic acid, and citric acid are found in ume.
Ume contains 74 compounds including “13 phenolic glycosides, 5 flavonoids, 15 flavonoid glycosides, 3 cyanogenic glycosides, 11 bezenoids, 8 organic acids, 2 furanic compounds, 4 phenylpropanoids, 4 triterpenes, 8 steroids, 1 diterpenes and 3 fatty acids” (Wu et al., 2011, p. 66). Mitani et al. (2013) report that the phenolic content is relatively high in ume fruits. This phenolic acid is recognized as an anti-inflammatory, antimicrobial, anti-carcinogenic, and antioxidant agent. In this regard, Mitani et al. (2013) stress that the ume fruit’s phenolic properties may have the ability to lower the risks of some chronic diseases. Gursoy and Tepe (2009) and Shi, Gong, Liu, Wu and Zhang (2009) also note that ume fruits have phenolic compounds that enhance anti-mutagenic, antioxidant, and anti-cancer activities. Adachi, et al. (2007) state that ume is abundant in minerals such as iron (crucial for blood forming), silicon (fundamental for healthy skin and hair), and beta-carotene (a great antioxidant).

Ancient people recognized the health benefits of ume long before modern science began and researched those benefits. More than a thousand years ago, Tanba (as cited in Hokari et al., 2012; Kurishima, 1997) wrote the first medical text in 984 in Japan and introduced the benefits of ubai (dried smoked ume originating in China) and umeboshi, a salted pickled ume which was developed in Japan. The effects are reducing fevers, counteracting nausea, and easing pain in the limbs; producing more saliva, curing diarrhea, improving the lung function, improving rough skin, and the detoxifying of food. Tanba (as cited in Kurishima, 1997) records that ume is sour, which warms up the body and harmonizes the liver and heart to produce relaxation effects. In addition to these numerous health benefits, Mitani et al. (2013) note that anthelmintic and antitussive effects have been recognized in ubai.

Tanba (as cited in Hokari et al., 2012; Kurishima, 1997) introduces the effects of salted pickled ume which is called umeboshi. The benefits, other than anti-diarrhea, are protecting the
heart, reducing fever, controlling pain, detoxifying, and improving rough skin. Tanba (as cited in Hokari et al., 2012; Kurishima, 1997) also notes that emperor Murakami dramatically recovered from an epidemic after he took kombu-cha with umeboshi. Most likely, Matsumoto (1998) explains, umeboshi was only available for noble people at that time. In the Kamakura period which was in the 1200-1300s, ume was used as food provisions by samurai warriors (Kishima, 1999). Finally, Kishima (1999) notes that umeboshi became widely available for common use in the Edo period which is around 1600’s. Umeboshi has been used for millennia, and this is the first recipe recorded in the book. Hirano (as cited in Matsumoto, 1998) introduced an umeboshi recipe in his book Honchosyokukan in 1697. In this recipe, ripened ume fruits are soaked in water and put into jars with salt for a couple of days until the salted juice comes out. Then, they are taken out of the jars and exposed to the sun. In the evening, the ume is put back into the salted juice in the jars. This procedure is repeated two or three times until the ume fruit becomes dry and wrinkly. Then, the ume is put back into jars with shiso leaves in order to produce a delicately flavored umeboshi. This product will last years when kept in the jars.

According to Mitani et al. (2013), umeboshi is a traditional and popular Japanese food used often as a preservative in other food items. It is also effective in treating fatigue, diarrhea, and fever. Fujita, K., Hasegawa and Fujita, M. (2002) and Mitani, Uchiyama and Saito (1985) emphasize that ume contains medical benefits, including antibacterial and fungicidal properties. Mitani et al. (2013) and Okubo (2013) also report that since ume fruit contains an abundance of citric acid, and citric acid improves appetite even on a hot summer day, umeboshi is a popular food in Japan. A typical Japanese lunch has one umeboshi in the middle of white rice with side dishes in an effort to prevent decaying food and boost one’s energy. Even 100-year-old
umeboshi is still edible according to folklore. Umeboshi can be preserved for a long period of time because of its organic acids, including citric and phosphoric acids (Vann, 2007).

In 1817, Kinutome (as cited in Hokari et al., 2012; Matsumoto 1998) states that *Shokokukodenhiho* is a folk remedy book in Japan. In this book, Bainiku Ekisu (BE), which is concentrated ume juice based on ubai, was introduced. BE was used to reduce fever and also was effective for treating dysentery, typhoid fever, food poisoning, diarrhea and indigestion. According to Fujikawa (1969), cholera was prevalent in 1822 and 1858 in Japan, and people depended on umeboshi and BE for prevention of cholera. Umeboshi and BE played a very important role during these epidemics.

Nakajima, Fujita, Inoue, Nishino and Seto (2006) stress that BE has been used as a Japanese folk remedy for more than a thousand years. The recipe of BE is as follows: one kg (2.2 lbs.) of ume is hand-grated off of the seed, and then grated material is filtered through a thin, durable Japanese hand towel, and the filtrate is boiled down for a couple of hours at 90°C (194°F) to 100°C (212 °F) to retrieve 20 g (0.7 oz.) of semi-solid ume called BE (Adachi et al. 2007). Therefore, the ratio is 50:1, the amount of raw fruit to final product (Adachi et al., 2007; Chuda et al., 1999). BE contains 60% citric acid, so it will last a long time at room temperature (Matsumoto, 1998).

**Recent Discoveries of Health Benefits in BE**

Recently, scientific studies discovered some key compounds and constituents, or mechanisms of health enhancing evidence of BE (Matsumoto, 2000). They are MK615, mumefural and many more. Other compounds and constituents certainly exist, but so far research has not identified the potential health benefits. This section is divided into three categories. They are titled MK615, mumefural, and general BE benefits.
MK615. First, the effects of MK615 are discussed. MK615 is produced by neutralizing BE with NaOH, then heat-sterilizing it (Hokari et al., 2012). The health benefits of MK615 are as follows: it has an anti-cancer, anti-inflammatory and anti-oxidative effects, as well as an anti-microbial and anti-bacterial effects.

Anti-Cancer effects. More studies of anti-cancer agents have been conducted compared to other pathologies. Nakagawa et al. (2007) claim that MK615 contains several triterpenoids that show antineoplastic (preventing or inhibiting the growth of cancers) effects. Nakagawa et al. (2007) experimented with the inhibition of breast cancer cell growth using MK615 in vitro and report that MK615 effectively inhibited the proliferation of breast cancer cells (MDA and MCF7 cells), presumably through apoptosis induction and cell cycle modification.

Tada et al. (2012) found that MK615 causes the death of A375 melanoma cells through the inhibition of ERK1/2-Id-1 pathways. Development of new treatments are necessary since chemo, radiant therapy, and immunotherapy are not effective (Tada et al., 2012). The group is still studying the mechanism and effectiveness of MK615 to be used as an adjuvant therapy for patients with malignant melanoma.

According to Hoshino et al. (2013), Adachi et al. (2007), Hiraishi et al. (2013), Al-Jahdari et al. (2011), MK615 has been reported to inhibit cell growth and induce the death of several tumor cell lines, including gastric cancer (Adachi et al, 2007), promyelocytic leukemia (Adachi et al, 2007), breast cancer (Nakagawa et al, 2007), pancreatic cancer (Okada, Sawada, Osawa, Adachi, Kubota, 2008), hepatocellular carcinoma (HCC) (Okada et al., 2007; Sakuraoka et al. 2010), colon cancer (Mori et al., 2007), esophageal cancer (Yamai et al., 2009), malignant melanoma (Matsushita et al., 2010; Tada et al., 2012) and lung cancer cells (Sakuraoka et al., 2010; Sunaga et al., 2011).
Hoshino et al. (2013) address that the clinical efficacy and safety of MK615 for chronic liver disease. MK615 also has anti-tumor effects against hepatocellular carcinoma (HCC) (Hoshino et al., 2013). One case report found that a patient with stage IVB hepatocellular carcinoma showed a decreasing alpha-fetoprotein (AFT) level as well as decreasing pulmonary and lymph node metastases after taking MK615. This patient survived for more than 17 months after administering MK615 for three months as a final alternative therapy without any other conventional treatments. None of the other conventional cancer treatments were effective for this patient. MK615 appears to exert an anti-tumor effects on HCC. Although it requires more studies, MK615 is a promising anti-cancer agent without causing serious negative effects.

**Anti-inflammatory and anti-oxidative agent.** According to Hokari et al. (2012) inflammation and oxidation may cause serious diseases, and MK615 could be a key compound for treatment. One example is that Hokari et al. (2012) stress that MK615 contains triterpenoids; these compounds exert anti-inflammatory and anti-oxidative effects that protect the liver in both animal models and clinical trial.

The mechanism of anti-inflammatory and antioxidative effects are described as follows. High-mobility group box 1 protein (HMGB1) plays a major role in numerous inflammatory disorders such as sepsis (Ito et al., 2007). According to Kawahara et al. (2009), an extract of ume is a great source of triterpenoids that strongly suppresses HMGB1, and Hokari et al. (2012), Kawahara et al. (2009), Morimoto et al. (2009) note, for these reasons, ume extracts work as an anti-inflammatory and anti-oxidative agent.

Several triterpenoids in MK615, such as oleanolic acid and ursolic acid, may have both anti-inflammatory effects and anti-cancer effects (Morimoto-Yamashita et al., 2012; Okada, Sawada, Osawa, Adachi & Kubota, 2007). Morimoto-Yamashita et al. (2012) suggest that
further research of natural sources of triterpenoids assure the treatment of life threatening systemic inflammatory disorders. In relation to this issue, Jemin and Salomon (2006) report that periodontal diseases associated with cardiovascular disease, osteoporosis, and diabetes mellitus. However, Morimoto-Yamashita et al. (2012) state that overusing antibiotic treatments for periodontal diseases may contribute to antibiotic resistance of these bacteria. As a result, creating new treatments for periodontitis may adequately inhibit systemic inflammatory diseases.

**Anti-microbial and anti-bacterial agent.** In the related previous section about periodontitis, Morimoto-Yamashita et al. (2011) conducted a study to investigate the anti-microbial effect of MK615 against oral bacteria. Their findings concluded that MK615 contains a number of organic acids to treat and prevent periodontitis and dental caries by inhibiting both growths of oral bacteria and biofilm formation. Morimoto-Yamashita et al. (2012) also stress that MK615 is a useful oral therapy treatment, such as toothpaste and mouth rinses. In addition to these effects, it may be effective for treating *Staphylococcus aureus* and *Candida albicans*. According to Cherrington, Hinton, Mead and Chopra (1991), and Tamblyn and Conner (1997), both citric acid and malic acid, found in ume, contain pharmacological benefits, such as anti-microbial, anti-bacterial, and anti-oxidative activity. According to Seneviratne et al. (2011), although anti-fungal activity was not detected, ume extract may possibly be used to develop an oral antimicrobial factor to prohibit or control dental disorders related to oral pathogenic bacteria. Seneviratne et al. (2011) also emphasis that ume could be a key ingredient of antimicrobial drugs since antimicrobial drug resistance is a primary global challenge these days.

**Mumefural.** Mumefural (MF), is a compound that is produced when citric acid and glucose chemically react in the heating process of making BE. The health benefits of MF are as
follows: a blood fluidity effect, an inhibitory effect on the pandemic influenza A (H1N1) virus, and an improvement on energy metabolism.

**Blood fluidity effect.** Blood fluidity is the ability for blood to flow easily through blood vessels. Chuda et al. (1999) discovered a novel compound called mumefural. This compound and the endogenous organic acids, citric acid and malic acid, in BE considerably improved the blood fluidity by using microchannel instruments for model capillaries. Matsumoto (2000) stresses that MF is only found in BE and Chuda et al. (1999) explain that it is produced during thermal processing.

**Inhibitory effect on pandemic influenza A (H1N1) virus.** Sriwilaijaroen et al. (2011), isolated five components from BE and examined their inhibitory activities against the novel influenza A/Narita/1/2009 (H1N1) pandemic virus. The result showed that mumefural worked most effectively as an anti-sialidase and anti-hemagglutination agent. The results suggest that mumefural might be a main compound for the development of an influenza A inhibitor. It not only improves blood fluidity, but may also reduce influenza A infection. In addition, molecular seed may be capable of being used as new anti-influenza inhibitors.

Although research conducted by Yingsakmongkon et al. (2008) did not identify a specific compound, Yingsakmongkon et al. (2008) report that BE may work to prevent and reduce infection by human influenza A virus in Mardin-Darby canine kidney (MDCK).

**BE benefits without identifying specific compounds.** This section discusses studies conducted using BE without identifying compounds. BE suppresses *Helicobacter pylori (Hp)*, improve stomach ulcers related to stress, improve the symptoms of diabetes, and show clinical potential to prevent osteoporosis.
Treating *Helicobacter pylori* (Hp). In 1994, the World Health Organization/International Agency for Research on Cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1994) announced that *Helicobacter pylori* (Hp) is a positive carcinogen based on the epidemiological discovery. Graham (1998) and Huang and Hunt (1999) note that current treatment is effective for 90% of patients, but 10% of patients remain Hp positive because of antibiotic resistance and other reasons. One of the benefits of BE is to suppress Hp, according to Otsuka et al. (2005). The study states that the specific substance that suppresses Hp is not identified yet, however, BE may have potential as a safe and cost effective natural medicine to manage Hp-related gastric disorder and gastric neoplasia.

Nakajima et al. (2006) conducted an in vivo pilot study for the effectiveness of BE on Hp infection in the human stomach. Although 5 out of 14 subjects had improved symptoms at 12 weeks, the Hp bacteria were not fully eradicated with BE. Administering procedures need to be evaluated for a future study.

**Improving stomach ulcers related to stress.** Examining rats’ ulcers, Kishikawa et al. (2002) learn that in rats that received BE, stomach epithelium started to regenerate. On the other hand, ulcers were widely spread in the ones that did not receive BE. Kishikawa et al. (2002) report that they supported BE as an effective treatment for stomach ulcer, although only partial recovery was observed in this five-week study. More than 5-week study needs to be done to observe more improvement.

**Improving the symptoms of diabetes.** Kishikawa et al. (2003) discovered that both rats that had 1% BE in water or who ate food with 2% BE lost some weight. Particularly, having BE in the drink maximized the benefits. In fact, diabetic rats that drank 1% BE-added water had
decreased triglyceride and blood sugar levels. The data clearly showed the improvement of high blood sugar levels.

**Clinical potential for preventing osteoporosis.** Water-soluble BE extract was used in this study. Bone mass is maintained by constant bone formation accomplished by osteoblastic cell activity and bone resorption performed by osteoclast cells. However, when one suffers from osteoporosis, bone mass decreases, causing bone fragility (Kono et al., 2011). Kono et al. (2011) conducted the experiment to examine the effects of ume extract on the reproduction and osteoblastic differentiation of osteoblastic MC3T3-E1 cells. The results show that water-soluble ume extract accelerates the proliferation and differentiation of osteoblastic MC3T3-E1 cells. Kono et al. (2011) stress that water-soluble BE extract contains citric acid, chlorogenic acid, malic acid, and 5-hydroxymethyl1-2-furfural. These components and other unknown components might increase osteoblastic differentiation. For these reasons, Kono et al. (2011) conclude that water-soluble BE extract stimulated the proliferation of cells and may have the potential to inhibit osteoporosis.

Another recent study conducted by Yan et al. (2014) reports that 23 compounds of ume were evaluated, and they discovered that six compounds remarkably trigger the pre-osteoblast differentiation in MC3T3-E1 cells. On the other hand, 11 compounds remarkably suppress the pre-osteoclastic differentiation in RAW264.7 cells. In conclusion, ume could be an excellent source of phytochemicals, which act as an anti-osteoporosis agent. After that Yan, Lee, Li, Jang and Kim (2015) discovered that 10 compounds remarkably inhibit osteoclastic RAW264.7 macrophage cell activation. These results present that ume would be a great food for preventing osteoporosis.
Recent Discoveries of Health Benefits in Ume using Different Processing Techniques

Some research groups investigated different techniques for processing ume, to identify its health benefits. These studies have shown that ume provides the following effects and benefits: anti-oxidative effects, infertility treatment, alleviation of oxidative stress and induction of skin carcinogenesis, antimicrobial effects, treating *Helicobacter pylori* (*Hp*), a laxative effect, use as a chemotherapeutic and anti-gout agent, inhibits development of atopic dermitis and melanogenesis, an antihypertensive effect, alleviates exercise-induced fatigue and improving energy metabolism.

**Antioxidative effect.** According to Xia et al. (2010), the well-known cause of obesity, aging, diabetes, cancer, and coronary heart disease is due to oxidative damage of organic molecules in the body. Xia et al. (2010) reported that chlorogenic acids, chlorogenic acid isomers, neochlorogenic acid, and cryptochlorogenic acid have antioxidant activity in the ethyl acetate essence of ume. A recent study conducted by Yan et al (2014) isolated 23 compounds from ume, of which 11 compounds are in the phenolic hydroxyl category; those particular compounds showed possible antioxidant activities. The latest study conducted by Zhang et al. (2015) identified 78 compounds within the ume flower, two of which have anti-oxidative effects.

**Anti-oxidative effect and potential infertility treatment.** According to Kono et al. (2014), granulosa cells shape ovarian follicles and play key roles in the maturation of oocytes. Therefore, the beneficial therapy for female infertility is to keep granulosa cells from oxidative stress cellular injury. Methanol extract from the ume seed, 3,4-Dihydroxybenzaldehyde (3,4-DHBA), has high anti-oxidative effects that suppress H_2O_2-induced apoptosis of granulosa cells. 3,4 DHBA also enhances estradiol secretion in granulosa cells and promotes the mRNA expression levels of steroidogenic factor 1 which is a promoter of crucial steroidogenic enzymes.
In addition, 3,4-DHBA may contribute to the development of excellent quality oocytes by activating granulosa cells. These findings indicate that ume seed may have the potential to prevent and treat female infertility.

**Alleviation of oxidative stress and induction of skin carcinogenesis.** According to Reuter, Gupta, Chaturvedi and Aggarwal (2010), although the body has defense mechanisms against oxidative stress, a decrease in antioxidant protection occurs when long-term exposure to sun or the process of aging. This causes oxidative damage to nuclei, lipids and protein that leads to many illnesses including cancer. Lee et al. (2013) found that fermented ume with probiotics can inhibit the formation of 7,12-dimethylbenz[a]anthracene (DMBA), 12-O-teradecanoyl phorbol 13-acetate (TPA) induced mouse skin carcinogenesis through decreasing of lipid peroxidation, improving total antioxidative capacity with an elevation of SOD (detoxification enzymes) levels.

**Antimicrobial effect.** Chen et al. (2011) report that aqueous extract of ume shows antimicrobial effects on *S. mutans* biofilm that is covering orthodontic brackets conducted in vitro. This result indicates that ume extract has the potential to be used as an antimicrobial agent for oral care for orthodontic patients.

Wong et al. (2010) evaluated 20 traditional Chinese medicines against bacteria in oral biofilms. They found that aqueous extracted ume had stronger antimicrobial activity than conventional mouth rinses against *S. mitis, S. sanguis, S. mutans* and *P. gingivalis* in vitro.

**Treating *Helicobacter pylori* (*Hp*).** A recent study investigated the inhibitory effect of dried ume or umeboshi against *Hp*. Enomoto et al. (2010) investigated the effect of having a high intake of ume (either more than three dried umes or salted pickled umes daily) to inhibit *Hp* infection and reduce active mucosal inflammation by evaluating 68 non-elderly volunteers. The
results indicated strong correlation between high ume intake and inhibition of \( Hp \) infection and reduction of active mucosal inflammation. They also found non-elderly \( Hp \)-positive participants’ antibody titers were remarkably lower in the high-intake group. According to Shimizu et al. (1999), higher antibody titers are related to higher incidence of gastric cancer. This result indicates that high intake of ume in earlier life has the likelihood of preventing gastric cancer and CAG progression. (Enomoto et al., 2010).

**Laxative effect.** According to Na et al. (2013), both unripe and ripe ume were sufficient in triggering automatic contractions of the rat colon. Particularly, ripened ume was effective due to the increasing citric acid content in the process of ripening ume fruits which enhances spontaneous colon contraction. This study confirmed that ume is effective in preventing constipation and therefore has therapeutic laxative effects in rats.

**Chemotherapeutic agent.** Park et al. (2011) explored the potential of ethanol extract of ume (EEU) as a chemotherapeutic agent by using human leukemia U937 in vitro and testing an ethanol extract of ume. Apoptosis is the scheduled cell death that naturally occurs within tissues. During cancer therapy, it is important to regulate apoptosis to maintain homeostasis. Although they could not identify a specific compound, EEU seems to trigger the enzyme caspase-3 that plays a key role in initiating and executing the apoptosis of human leukemic U937 cells.

**Anti-gout agent.** Yi, Li, Su, Dong and Li (2012) report that methanol extract from ume (MEU) has a hypouricemic effect in mice and Yi et al. (2012) speculate that MEU may be a mediator to inhibit Xanthine oxidase (XO) activity in the liver. According to Kawahara et al. (2009) and Yamai et al. (2009), MEU consist of several triterpenoids, such as oleanolic acid, ursolic acid, lupeol and \( \alpha \)-amyrin. According to Sudharsan, Mythili, Selvakumar and Varalakshimi (2006) and Singh, Bishnoi, Agarwal and Bhatt (2011), lupeol and its extract
lowered serum uric acid in hyperuricemia-like rats and nephrolithiasis patients reducing gout occurrences. Yin and Chan (2007) note that oleanolic acid and ursolic acid contain XO inhibition activity in vitro. For these reasons, Yi et al. (2012) hypothesize the hypouricemic effect of MEU could be attributed to the triterpenoids. They conclude that MEU could be a strong candidate for an anti-gout agent for clinical utilization.

**Effects on atopic dermitis and melanogenesis.** According to Jung, et al. (2010a), fermented ume with probiotics (ume juice mixed with nonfat rice bran and *Saccharomyces cerevisiae*) may have the potential effect of suppressing the development of atopic dermatitis (AD). They observed that significantly decreased clinical skin conditions and mild dermal and epidermal inflammation changes on DNBC-treated NC/Nga mice that administered 2% fermented ume compared to the control group. In addition, serum IgE concentration and eosinophil ratios were remarkably reduced as well as *Staphylococcus aureus* colonies. Since the fermentation process is complex, they have not identified constituents or compounds; however, they found that fermented ume with probiotics can suppress expansion of AD-like skin area in NC/Nga mice, possibly through the induction of IL-10 inhibits or suppression of macrophage or T-cell responses. Nakamura et al (2013) discovered that acylated quinic acid analogs 6-4, which is a methanol extraction from ume flower buds, inhibited melanogenesis without activating cytotoxicity. They concluded that ume with probiotics is promising for treating skin disorders.

**Immune-enhancing effect against Bordetella bronchiseptica.** Jung, et al. (2010b) found that levels of antibody production improved remarkably against *Bordetella bronchiseptica* (leads to infectious bronchitis in mostly animals) in the fermented ume with probiotic fed group of mice. The results show that maintaining ingestion of fermented ume with probiotics improves immunity against *B. bronchiseptica* infection in mice. Since there is a worldwide concern of
overuse of antibiotics, this may be a good alternative medicine to reduce usage of antibiotics in animals.

**Anti-hypertensive effects.** Takemura et al. (2014) conducted a double blind randomized placebo-controlled pilot study for 15 participants with blood pressure concerns for a duration of 12 weeks by examining blood pressure. Umezu polyphenols (UP) were administered for the control group. The results show no significant difference between the UP-ingesting group and the placebo group. Takemura et al. (2014) conclude that they found UP is safe to consume in higher doses, and a larger sample size study needs to be done to further investigate the effectiveness of UP for antihypertensive effects.

**Alleviate exercise-induced fatigue.** According to Kim, Lee, Park, S.H. and Park, T. (2008), taking water extract of ume in the time of endurance exercise could improve “the oxidative capacity of exercising skeletal muscle and may induce the muscle to prefer fatty acids for its fuel use rather than amino acids or carbohydrates” (p. 460) in mice in vivo experiment. More research can be done in this area.

**Memory-improving and anti-depressant effects.** Kim, Ha, Kim, Park and Lee (2008) found that a mixture of ume concentrate, disodium succinate and span80 (3.6: 4.6: 1 ratio) enhances memory, learning ability and improves anti-depressant effects when administering to normal rats daily (460 mg/kg) for 3 weeks. This mixture treatment activates MAPK/ERK signaling pathways in the hippocampus in rats which improves learning ability, memory and acts as an anti-depressant.

**Effects on diabetes and obesity.** According to Shin et al. (2013), ethanol extract ume contains flavonoids that are a potential treatment of diabetes and obesity. Flavonoids are able to control glucose metabolism by coordinating PPAR-γ activation and withholding fat
accumulation in mice fed a high fat diet. Unlike glitazones, ethanol extract ume does not show any side effects, such as increasing body weight and cardiovascular risks (Nissen & Wolski, 2007; Singh & Segal, 2012).

**Effects on energy metabolism.** Ko, Kim, Kang, Ryuk and Park (2013) conducted the study of the combination of ume extract and *Lithospermum erythrorhizon Sieb. Et Zucc*, which is a traditional Chinese herb, synergistically prevented the malfunction of energy expenditure, restoring normal glucose, and lipid metabolism in ovariectomized rats. This study simulated a menopausal state which led Ko et al. (2013) to indicate that it may be effective for alleviating the metabolic disturbances associated with menopause.

**Summary**

Ume has been used as a remedy and food for thousands of years in Japan and other Asian countries. Although ume originally came from China, the Japanese people have used ume and passed on its health benefits from generation to generation. Ubai, umeboshi and BE have been used for numerous health ailments, and these benefits were recorded in ancient medical text books. Modern people in East Asia still use ume as a folk remedy.

Recent studies show ume has potential health effects which include anti-cancer, anti-inflammatory, anti-oxidative, antimicrobial, antibacterial, and blood fluidity effects, as well as inhibitory effects on the pandemic influenza A (H1N1) virus; it also suppresses *Helicobacter pylori (Hp)*, improves stomach ulcers related to stress, improves memory and depressant conditions, and diabetes, and prevents osteoporosis. In addition, ume potentially could prevent and treat female infertility, lessen occurrences of gout, offer laxative effects, and inhibit the development of atopic dermatitis and melanogenesis. Finally, ume alleviates exercise-induced fatigue, improves energy metabolism and may be a potential chemotherapeutic agent.
Even though these numerous potential health effects have been discovered in recent studies, ume and BE-based foods, remedies and medicines remain largely unknown in the Western world. A systematic review of literature has not yet been conducted; providing one could increase awareness of ume and BE’s benefits. The research question emerging from this review is: What is the current, quality empirical research literature concerning the health benefits of ume and BE? Therefore, the purpose of this research is to systematically review the last 20 years of empirical studies on the health benefits of ume and BE in order to make any quality findings more accessible to the general public and health care providers.
Research Lenses

The purpose of this chapter is to articulate the relevant research lenses that have influenced the progress and completion of this study. The articulation of these lenses is needed to describe the ways in which I view the world because this directly impacts the research. These relevant lenses influence my research topic, question, purpose, method, data collection, and analysis.

First, I begin to explore how my research paradigm and culture of inquiry frames this research project. Next, I explain my theoretical, professional, and personal lenses and how they influence this study.

Research Paradigm and Culture of Inquiry

I am a post-positivist with a critical realist ontology and believe that there are always absolute facts that exist in this world. Although math and science are not my favorite subjects, when I solve the problems the answers are valid and replicable, and these facts are undeniable and conventional. I believe in concrete natural laws; however, human intelligence and sensory perceptions are limited in their ability to obtain everything that exists in this world (Guba, 1990).

With a post positivist epistemology, maintaining objectivity is the ideal during the research process. Since I am a solo researcher, eliminating bias is a challenge. I have to constantly remind myself of those biases to ensure each step is done as objectively as possible.

I believe in experiments done in both natural settings and controlled settings. For example, people have experimented with in daily life for thousands of years to reveal their benefits of folk remedies. Some people might have lost their lives because they ate raw unripened ume. On the other hand, some desperate people might have recovered from a terminal illness by taking processed ume accidentally. In another situation, a family ate 100 year-old
umeboshi accidentally and discovered they were still edible and had been preserved well (T. Miyazaki, personal communication, July 20, 2015). East Asian people rely on these thousands of years of accumulated experience, and are likely why folk remedies get passed on from generation to generation. However, people who live outside of the East Asian norm have no idea about the benefits of ume and probably would not believe in this East Asian folk remedy since they are not familiar with ume. Therefore, it is necessary to use an empirical culture of inquiry to show scientific evidences of data and convey widely recognized methods to show the health benefits of ume and BE. In order to persuade people, I believe that experiments should be conducted in controlled environments, and the results should be replicable. Therefore, empirical culture of inquiry works to answer my research question. In order to become a more objective researcher, I should eliminate my subjective beliefs concerning the health benefits of ume. However, no matter how I carefully conduct research, it is almost impossible to obtain 100% accurate results.

After describing the theoretical lenses, I provide professional and personal lenses. These lenses will have an impact on the way the research develops and is interpreted. First, the professional lens informs my readers of the individual experience of my research and provides some background about my past and present professional and personal experiences.

Theoretical Lenses

Two main theoretical frameworks present the conceptual grounding for this research. They are Oriental Medicine and Empirical Theory. Oriental Medicine includes the following: Traditional Chinese Medicine, Kampo Medicine (a traditional Japanese medicine), and Traditional Korean Medicine. First, I will discuss Oriental Medicine and how it was developed.
along with Traditional Chinese Medicine, Kampo Medicine and Traditional Korean Medicine. Next, I will present Empirical Theory.

**Oriental Medicine.** According to Cha et al. (2007), Oriental Medicine is known as an accumulation of medical knowledge obtained from different places throughout East Asian countries. Repeating substantial trial and error has contributed to systematized knowledge and transformed into the medicine of present-day. There are several reasons that Oriental Medicine has distinctive characteristics by region (Cha et al., 2007). Locally grown natural herbs are used as medicine, epidemics and diseases differ with geography and environment, and the observation of differences in illnesses clearly stands out in such places as Korea, Japan and China. These countries built their own geographical, cultural and linguistic environments (Cha et al., 2007). All included research articles in the systematic reviews are from China, Japan and Korea, and in each country their way of processing ume is unique. This fact influenced my perspective to consider extracting the information found in each article about how these countries process ume.

**Traditional Chinese Medicine (TCM).** Traditional Chinese medicine (TCM) has about 5000 years of history (Gao, 1997). TCM is a highly sophisticated philosophy includes the concept of yin and yang (one’s existence related to others, as well as contrasts such as slow and fast), and five transformative phases which consider the universe to be made up of five elements including wood, water, metal, fire and earth. Each element is also figuratively described as a physical part, and every part is interrelated with harmony (Gao, 1997). TCM treats each person as a whole (mind, body and spirit); therefore, TCM integrates various treatments such as herbal therapies, food as therapy, Qi gong, acupressure and acupuncture (Gao, 1997). From this perspective, ume was used as a medicine as well as a food. Individual elements of Traditional Chinese Medicine have been known in the Western world, such as Qi gong and acupuncture;
however, herbal medicine from the Eastern world has not been widely recognized yet. By presenting a systematic literature review of the health benefits of ume, readers will learn the long history of ume as medicine and food as well as its many health benefits from this perspective.

**Kampo Medicine.** According to Watanabe et al (2010), Japanese traditional herbal medicine, known as Kampo, originated during the Han period (206 BC to 220 AD) in ancient China. It has more than 1500 years of history in Japan. During the Edo-period from 1600, the specific Japanese feature of Kampo was formed during the time that Japan closed the door to foreign countries. Eshima, Yokoyama, Abe, Hayakawa, and Saiki (2015) state that currently, physicians who were trained in Western Medicine also recommend Kampo Medicine in Japan.

Watanabe et al. (2010) report that compared to the highly theoretical nature of Chinese Medicine, Kampo is more practical. Kampo practitioners prescribe a combination of multiple natural medicines according to each patient’s symptoms. “Kampo has a holistic therapeutic approach, as the mind and body are seen as one entity. The therapeutic aim is to relieve symptoms and to restore harmony in bodily functions” (Watanabe, et al. 2010 p.2). In addition, Yamanouchi and Yamagami (1987) state that Kampo works slowly in one’s body, but surely improves the physical condition in many different areas to harmonize one’s body without any side effects. This herbal practice was widely accepted among people and became a part of folk remedies. According to Yamanouchi and Yamagami (1987), ubai, which is smoked dried ume, first came to Japan from China more than 1000 years ago and has been used as Kampo since then, and later became popular as a folk remedy.

I believe that harmonizing bodily functions to restore health is one of the special features of natural medicine including ume. More than a thousand years of accumulated ancient knowledge and clinical trials have proven that it is a safe and effective treatment in Japan. To
make its health benefits more accessible to the Western world, a systematic review of literature is effective. Since I grew up in Japan and have some knowledge of Kampo medicine, this influence my literature search, implementation and interpretation of data.

*Traditional Korean Medicine (TKM).* Traditional Korean Medicine is not widely recognized. I did not know about this medicine until I started this research project. Around the 10th century, TCM was introduced to Korea. Korea was able to use accumulated knowledge of Chinese Medicine without a trial-and-error period (Cha et al., 2007). In the late period of Korean dynasty, life expectancy dramatically increased as an understanding of Korean natural herbal medicine increased. By the 15th to the 16th centuries, the foundation of TKM was developed (Cha et al., 2007). In addition, Korea began to interact with the West only after WWII, which is very different from China and Japan. For this reason, TKM has been preserved well (Yeonseok, 2011). Traditional Korean diets incorporate many different fermented foods such as soybean products and kimchi (Kim, Koh, Chung, & Kwon, 2000). I learned that fermented ume with probiotics is part of the traditional Korean diet throughout this research project. Since eight articles are from Korea, and some studies showed the health benefits of fermented ume, TKM influence the results of this study.

*Empirical study.* Although Oriental medicine has a long history and people from Asian countries are more familiar with it, it is still not widely recognized in Western countries, where acceptance of Western culture and empirical study currently dominates accepted knowledge. Physical activities, such as yoga and tai-chi, have become more accessible in the West; however, Western people might be more cautious and skeptical about ingesting foreign medicine or food without ample empirical evidence or broad cultural acceptance. Therefore, showing evidence of the health benefits of ume is the best way to persuade people who are not familiar with ume.
According to the J. Murrey Atkins Library (2010), empirical research is based on observation or experimentation to answer a precise question or to experiment on a hypothesis. Bradford (2015, March) stated that researchers documented and analyze data either to prove or disprove a precise hypothesis. In my systematic review of literature, I will review empirical research literature that shows the results of potential health benefits by presenting either the effects of specific compounds or constituents, or by explaining the mechanism of treating certain symptoms. Presenting these specific facts will be strong evidence to persuade the readers.

**Professional Lens**

I have a master’s degree in Recreational Therapy and have worked within the field of Recreational Therapy with an elderly population. I also taught Japanese including Japanese calligraphy to elementary school students, high school students and college students. Currently, I am working on a Master of Arts in Holistic Health Studies Program at the University of St. Catherine. I was surprised to learn that what I was eating regularly in Japan—including green tea, soy beans, ume and azuki—was listed as healthy food in our textbooks. I also learned the concept of food as medicine which I had been practicing all my life without knowing this concept. I felt that I discovered treasure, and I had a passion to share more knowledge of Japanese foods with others. Since ume is not widely recognized in the Western world, and I know from my experience that ume has many health benefits, I decided to investigate scientific evidence about ume in the context of my master’s studies. Although biomedical field is not my expertise, I did my best to examine how ume influence on one’s body; I also examined how ume was processed according to each country’s tradition because different processing methods could impact compounds and constituents in ume. Both modern scientific perspective and oriental medicinal perspective influence my project’s design, implementation and interpretation.
Personal Lens

I was born and raised in Japan. For my generation in Japan, family consisted of an extended family which included my parents, my younger sister and grandparents. In Japan, elderly people are highly respected. Consequently, my grandparents were the source of family knowledge. Grandmother told us many folk stories and cooked some traditional Japanese meals. Grandfather taught us crafts and some Japanese history. One of our family traditions was to harvest ume fruits from our backyard. My grandmother made umeboshi and umeshu (ume wine). We all considered ume as daily food as well as medicine. We ate umeboshi with rice daily. For lunch, most people in Japan put umeboshi in the middle of rice and called it a Japanese flag lunch box. We have been told that umeboshi is a natural preservative, pain killer, fatigue recovery medicine and medicine for longevity. When we had a headache, we were told to put umeboshi around the temple area to relieve pain. During hot summer days, we were allowed to drink diluted ume wine to prevent heatstroke. I actually did not know anything about Bainiku-Ekisu (BE) until 10 years ago. My mother brought BE from Japan when my son was born. My mother recommended I use this when I am sick or tired. As my son got older, he began to enjoy BE’s tart taste and he started taking it daily, as did I. I noticed that I had more energy and rarely got sick after starting to take BE daily and it had same effect on my son as well. Even my dentist said that my gum pocket condition is better than before.

I always wondered why ume has many health benefits. To investigate my personal question, my design, implementation and interpretation of this study was focused on discovering the health benefits of ume.
Method

The purpose of this research is to systematically review the last 20 years of empirical studies on the health benefits of ume and BE in order to make any quality findings more accessible to the general public and health care providers. In order to systematically collect credible data to evaluate and critically analyze, I chose the systematic review of literature method framed in an empirical research culture of inquiry.

This chapter includes a rationale and description of systematic review of the literature method. Next, it includes a preliminary description of the process including sampling, data collection, data analysis and synthesis, reliability and validity and ethical considerations. Finally, it closes with a discussion of strengths and limitations related to this study.

Rationale for a Systematic Review of Literature

Ume has been used as food and medicine for thousands of years in the Asian world. People processed ume for daily usage, through fermentation, salting, heating, alcohol soaking (Hokari et al. 2012; Kim, Lee, Park, S. H., Park, T., 2008; Matsumoto, 1998; Mitani et al., 2013; Vann, 2007). However, it is not widely recognized in the Western world. Recently, researchers discovered that ume contained possible health benefits in the labs, animal studies, and a few clinical trials. Despite recent studies showing numerous health related benefits of ume and BE (Ko et al., 2013; Mori et al., 2007; Seneviratne et al., 2011), their health benefits are not popularly known, and no systematic review of literature exists. Therefore, the purpose of this research is to review systematically the last 20 years of literature of ume and BE in order to make that knowledge more accessible.

There are two reasons that I chose systematic review of literature. The first reason was that there is no systematic literature review of ume that has been conducted in the past. The
second reason was to be able to search an abundance of literature of health benefits of ume and collect numerous validated data to expand my knowledge and make it more accessible. Therefore, my aim is to find concrete evidence of various health benefits of ume and BE by using a systematic review of the literature.

Systematic review of the literature is widely used in the healthcare field, the education system, and other disciplines. Systematic reviews aim to collect a large quantity of high quality scholarly literature, by using academic databases and hand-searching, to analyze and synthesize the best feasible evidence relating to a precise research question to contribute knowledge and evidence-based answers (Boland, Cherry & Dickson, 2014). Therefore, through this method I can effectively searches high quality scholarly literature of ume and BE, and analyze and synthesize to collect as many credible data of those health benefits as possible.

In order to do a high quality systematic review of literature, it should be objective and transparent to eliminate bias and increase validity and reliability. Boland et al. (2014) explain the nine steps of literature review as follows.

Step 1: performing scoping searches, identifying the review question and writing protocol

Step 2: literature searching

Step 3: screening titles and abstracts

Step 4: obtaining papers

Step 5: selecting full-text papers,

Step 6: quality assessment,

Step 7: data extraction

Step 8: analysis and synthesis

Step 9: writing up and editing.
By taking each step carefully and documenting all information accurately, a systematic review of literature has potential to be credible.

**Sampling**

This section describes sampling procedures including the types of studies, materials and methods, results and search methods for identification of studies.

**Types of studies.** The types of studies are all empirical peer reviewed studies in English which examine the health benefits of ume and BE.

**Materials and methods.** Materials and methods in the studies include extracting particular compounds or constituents from processed ume (fruits, seeds or flower) under certain conditions (heated, methanol extracted, ethanol extracted, freeze dried, fermented, and aqueous extract), and were in vitro (cells, viruses and bacteria), in vivo (animals and humans), and in clinical trials (humans only). In addition, the data in the tables includes countries where the cells were from.

**Results.** Results include comparison between control group and experimental group of inhibiting bacterial activity, viral activity and cell growth after administering ume extract or BE. Another results the size of cell growth or the number of bacteria before and after administering ume extract or BE. Other results include analysis of chemically separated compounds to identify each activity such as anti-oxidant, anti-bacterial, anti-inflammatory, anti-osteoporosis, anti-viral, anti-cancer, and laxative effects, as well as stimulated proliferation.

**Search methods.** In order to search literature of health benefits of ume, I utilized MEDLINE, CINAHL, Alt Health Watch and Health Source Nursing/Academic Edition database. They are academic databases that collect academic journals and scholarly works. By using
credible databases, the credibility and validity of this research increases. I can also reduce bias by using databases because they collect data from a wide variety of sources.

In preparation for the systematic review of literature, I reviewed current literature of ume and BE by searching English language peer reviewed, full text published research articles and most up-to-date abstracts from January 1995-December 2015. Then, I typed these key words on databases:

1. “prunus mume” and “medicine or treatment” not “horticulture”
2. “concentrated prunus mume juice” and “medicine or treatment” not “horticulture”

By using key terms “prunus mume”, it covers both Prunus mume Sieb. et Zucc which is a scientific name and prunus mume that is commonly used in the studies. The term “ume” was not recognized as having the same meaning as Prunus mume Sieb. et Zucc by databases. In addition, by using “medicine or treatment”, I collected literature of biomedical and pharmacological studies that provide cause and effect, evidence based literature. I excluded articles related to horticulture. For these reasons, searching the key terms above provided the literature for my research.

Data Collection

This section discusses screening titles and abstracts, and obtained studies.

Screening titles and abstracts. My initial searches identified 62 references combining “prunus mume” and “medicine or treatment” not “horticulture”, and “concentrated prunus mume juice” and “medicine or treatment” not “horticulture”. I removed 29 duplicate articles by using Refworks software and I excluded three articles manually due to irrelevant titles. Then, I recorded all the search terms used for each specific search, the names of databases, the number of references identified by each search, the number of duplicates removed, and the number of
references that I checked in the process of screening titles (see Table 1, Table2, Table3) (Boland et al. 2014).

Table 1.

Collecting and screening articles using search terms: “prunus mume” and “medicine or treatment” not “horticulture”

<table>
<thead>
<tr>
<th>Database with dates</th>
<th>Search date</th>
<th>Number of hits retrieved from search</th>
<th>Number of articles discarded due to irrelevant titles</th>
<th>Number of articles duplicated from another database</th>
<th>Number of articles to be reviewed by title and abstract</th>
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</thead>
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<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2

Collecting and screening articles using search terms: “concentrated prunus mume juice” and “medicine or treatment” not “horticulture”

<table>
<thead>
<tr>
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<th>Search date</th>
<th>Number of hits retrieved from search</th>
<th>Number of articles discarded due to irrelevant titles</th>
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</table>
Table 3

Collecting and screening articles using search terms: Combined two searches

<table>
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</table>
Obtaining Studies. After completing the screening process, 30 articles remained. I screened all titles and abstracts by applying my inclusion criteria. My inclusion criteria is the literature that presents health benefits in the following areas: in vitro, in vivo or clinical studies, in addition materials, methods are clearly discussed. The purpose of this research is to study health benefits of ume, so I excluded any articles that do not present possible health enhancing content. Next I obtained a hard copy of full text papers. Then, I read full text papers to determine if the papers should be excluded or included. I excluded five articles, and I included 25 articles.

After obtaining 25 included articles, I corresponded with authors of those 25 articles. I emailed each author to ask about their newest research and findings. I wrote 13 Japanese authors in Japanese (see Appendix A), six of whom replied. I wrote Korean and Chinese authors in English (see Appendix B). One Chinese author did not supply any email address. I had not heard from any Korean or Chinese authors until I had the English message translated into Korean and Chinese (see Appendix C & D). After that, one email from Korea stated that email was no longer used, and another email from Korea stated that no new study had been conducted. No Chinese authors replied.

Of the Japanese authors, Mr. Enomoto is no longer conducting the same ume research project, but he supplied the newest research article that his group published, *Japanese Apricot Improves Symptoms of Gastrointestinal Dysmotility Associated with Gastroesophageal Reflux Disease*, published in 2015 (S. Enomoto, personal communication, January 24, 2016). Mr. Zeniya reported that his group discovered a new compound of ume, and they are preparing for a clinical trial (M. Zeniya, personal communication, January 25, 2016). Mr. Maruyama stated that Adabio, the company which sponsored his research, has more research information available. (I.
Maruyama, personal communication, January 30, 2016). After that, I searched Adabio online and found that 18 research articles related to health benefits of ume were listed on their website; these articles are all stored in the PubMed database. Mr. Kanekura did not have any new findings after he published two studies (T. Kanekura, personal communication, February 7, 2016). Mr. Suzuki’s group is still studying mumefural as an anti-influenza agent, and their goal is to produce a clinically proven anti-influenza medicine with BE. He also sent me his article *Mumefural and Related HMF Derivatives from Japanese Apricot Fruit Juice Concentrate Show Multiple Inhibitory Effects on Pandemic Influenza A (H1N1) Virus*, published in 2011 (T. Suzuki, personal communication, February 19, 2016). My database search with specific key words did not include Suzuki’s article.

Finally, I recorded 27 included articles including two articles which Mr. Enomoto and Mr. Suzuki recommended on Table 4 (see Appendix E, Table 4) and five articles that I excluded on the Table 5 (see Appendix E, Table 5). Characteristics of Excluded Studies, found at the end of paper including the reasons for exclusion (Boland et al. 2014).

**Data Analysis and Synthesis**

This section includes quality assessment, and data extraction.

**Quality Assessment.** The purpose of quality assessment is to evaluate each study’s reliability and validity (Bettany-Saltikov, 2012). In order to evaluate collected studies, including mostly a mixture of designs, I chose an assessment tool (see Appendix F, Table 6) created by Caldwell, Henshaw and Taylor (2011). Examples of questionnaires address the authors’ credibility, whether the context of the study is outlined, and whether the discussion is comprehensive. Quality assessment was a time consuming task; however, it was important to document quality-related assessment questions. This helped later to describe reasoning for the
included literature. Since quality assessment is usually designed to fill out checkmarks, it does not show the grey areas that often exist.

**Data extraction.** The process of data extraction provides the readers with an opportunity to fully understand the data both analytically and descriptively (Boland et al., 2014). The main purpose of data extraction is to answer research questions. Therefore, I reread all included studies and data extractions that were placed on the Table 4. My main interest concerning this systematic review was to obtain outcomes of health benefits of ume and BE from each empirical study, so I was particularly careful when reading the result sections to obtain accurate outcomes.

Finally, Table 4, Characteristics of Included Studies was filled out completely. Data includes years, authors, full papers or abstracts, methods, the types of processed of ume and BE, interventions, outcomes, countries and sponsorships. I recorded data both in handwritten notes and in an electronic version.

**Reliability and Validity**

In order to maintain reliability, each step should be replicable (Boland et al., 2014). By following each step carefully, researchers should reduce bias and increase reliability (Bettany-Saltikov, 2012). One thing that I did to increase reliability was to show all the steps of the systematic review, carefully conduct a quality assessment, and present extracted data. In order to increase the validity of my research, I used academic databases and contacted experts in this field to obtain the latest findings concerning the health benefits of ume and BE. I obtained two more articles directly from the authors who are experts in the field.

**Ethical Considerations**

Positive results are more likely to be published by authors for a professional journal publication (Boland et al. 2014). In my case, since I was searching positive findings in ume, I
tried to be objective by including as many credible studies as possible and by investigating authors and their positions carefully. In addition, since source of funding could sometimes influence the study results, I included sponsorship for data extraction and I placed in them Table 4.

**Design Specific Strengths and Limitations**

This section presents design specific strength and limitation.

**Strengths.** The strength of a systematic review is to learn and collect many validated findings to answer the specific question. Therefore, a systematic review is a practical way to present evidence-based answers, such as the health benefits of ume and BE. In addition, a systematic review is replicable and reliable by taking transparent steps including systematic search, inclusion/exclusion criteria, quality assessment of included studies, characteristics of included/excluded studies, and by presenting findings. Finally, I contacted all authors of included articles. Since Japanese is my first language, I was able to obtain detailed information from Japanese authors.

**Limitations.** Boland et al. (2014) suggest that research should be conducted by a group; however, in my case, I do not have any training in systematic review of literature, and I am conducting this whole project alone. I was as objective as possible; in order to eliminate bias or subjective judgement, but ideally, the literature review should have included two or more researchers. Moreover, although the contents of studies were all biomedical, I did not have any formal training in the biomedical field. These facts affected the quality of the study. In fact, study 18 (see Appendix E) describes technical information and I could only comprehend the Abstract. In addition to this, articles are limited to those written in English. Many results of
health benefits written in different languages could be missing from this systematic review of literature.
Results

The purpose of this chapter is to present the results of the study in order to answer the question: What is the current, quality empirical research literature concerning the health benefits of ume and BE? In order to answer this question, I conducted a systematic review of literature. I obtained 27 articles and did a quality assessment of the articles as well as data extraction. I also contacted all authors by email to search for the latest studies or findings.

The results of this study begin with a description of the 27 included studies. Next, I present the health benefits of ume and BE, then I describe the sponsorships of each article. Finally, I present the correspondence with the authors.

Description of Studies

Of the 27 articles, 15 studies are from Japan, eight studies are from Korea and four studies are from China. Of the 27 articles, 20 are in vitro studies, two are both in vitro and in vivo studies, one is both in vitro and clinical study, one is in vivo and clinical study and three are clinical studies only. Among the three clinical studies, two studies are cohort studies and one is pilot clinical study. Among the 20 in vitro studies, six studies report cells were purchased from the USA and two studies report cells were from Japan.

Description of Health Benefits

There were 10 included articles related to BE benefits. Among these 10 articles, seven articles discuss the efficacy of MK615 (BE extract). Its health benefits are as follows: anti-inflammatory (Hokari et al., 2012; Jung et al., 2010a; Kawahara et al., 2009), anti-oxidant effects, hepatoprotective effect in vivo (rats) (Hokari et al., 2012), anti-cancer effects on advanced hepatocellular carcinoma in a clinical study (Hoshino et al., 2013), advanced malignant melanoma in vitro study (Matsushita et al., 2010), colon cancer cells in vitro (Mori et al., 2007),
breast cancer cells in vitro (Nakagawa et al., 2007) and melanoma cells in vitro (Tada et al., 2012). MK615 also has anti-microbial efficacy against formation of *S. mutans* biofilm in vitro (Morimoto-Yamashita et al., 2011). Two research groups report BE having efficacy of inhibiting influenza A virus infection in vitro (Sriwilaijaroen et al., 2011; Yingsakmongkon et al, 2008) and Sriwilaijaroen et al. (2011) identified that mumefural, the compound from BE, inhibits influenza A virus infection. Kono et al. (2011) report that BE may have the potential to prevent osteoporosis as well.

The rest of the 17 articles identify health benefits in ume using different processing techniques. Five research groups describe specific compounds including oleanolic acid (fractionation of ume extract), 3,4 DHBA (methanol extract), citric acid and malic acid, acylated sucroses and acylated quinic acid (methanol extract), and flavonoids (ethanol extract). Kawahara et al. (2009) identified that oleanolic acid inhibits the release of HMGB1 from RAW264.7 cells. Kono et al. (2014) describe that the bioactive compound, 3,4-Dihydroxybenzaldehyde (3,4-DHBA), inhibits oxidative stress and enhances estradiol secretions in human ovarian granulosa tumor cells in vitro, and it may be effective for infertility treatment. Na et al. (2013) report that ripened ume contains citric acid and malic acid which have a laxative effect on constipation induced by a low-fiber diet in a rat model). Nakamura et al. (2013) discuss that acylated sucroses and acylated quinic acids analogs from the flower buds of ume have an inhibitory effect on melanogenesis. Finally, flavonoids which are found in ethanol extract ume have potential to prevent and treat diabetes and obesity (Shin et al, 2013).

Two research groups studied umeboshi (dried or pickled ume). Enomoto et al. (2010) report that high intake of dried or pickled ume has an inhibitory effect on *H. pylori* related active inflammation of the stomach and progression of chronic atrophic gastritis in a clinical study.
Maekita et al. (2015) explain that daily intake of one dried and pickled ume improves digestive dysmotility symptoms, leading to the relief of GERD symptoms.

Three research groups discuss that fermented ume with probiotics has an anti-inflammatory, immune-enhancing and anti-oxidative effect. The anti-inflammatory effect suppresses the development of atopic-dermatitis like skin lesions in mice (Jung et al., 2010a), enhances immunity against *B. brochiseptica* in mice (Jung et al., 2010b) and anti-oxidative effect could reduce skin carcinogenic activity in mice (Lee et al., 2013).

Three research groups state the traditional Chinese medicine method, aqueous extract of ume. This method has anti-microbial activity against common bacteria in oral biofilm in vitro (Wong et al., 2010). Also aqueous extract of ume contains the antimicrobial efficacy on *S. mutans* biofilm on orthodontic brackets in vitro (Chen et al., 2011). In addition, this method has antimicrobial activity against wide range of pathogenic oral bacteria in vitro (Senevirantne et al., 2011).

Two research groups explain how ethanol extract of ume exerts an anti-diabetic effect both in vitro and in vivo (Shin et al., 2013) and may be a potential chemotherapeutic agent to control human leukemia U937 cells (Park et al., 2011). Yi et al. (2012) stress that methanol extract from ume has hypouricemic efficacy that could develop an anti-gout agent.

Some studies use mixtures of formulation with ume. Kim et al. (2007) report the formulation of ume concentrate, disodium succinate, and Span 80 (3.6: 4.6: 1) shows significant improvement of memory in rats and Ko et al. (2013) indicate ume and *lithospermmum erythrorhizon* extract synergistically prevent the impairment of energy, lipid, and glucose metabolism by overiectomized rats.
According to the results, I documented more than 20 health benefits of ume/BE that organized by compounds and processing methods in Table 7.

Table 7

*Health benefits of ume organized by compounds and processing methods*

<table>
<thead>
<tr>
<th>Compounds or processed methods</th>
<th>Health benefits</th>
<th>Health issues/diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MK615 (BE extract)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triterpenoids including ursolic acid (UA), oleanolic acid (OA), lupeol, α-amyrin and β-sitosterol</td>
<td>Hepato protective effect</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory effect</td>
<td>Chronic inflammation of the liver</td>
</tr>
<tr>
<td></td>
<td>Anti-oxidative effect</td>
<td>Fatty liver disease</td>
</tr>
<tr>
<td></td>
<td>Anti-microbial effect</td>
<td>Dental caries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peridontitis</td>
</tr>
<tr>
<td></td>
<td>Anti-cancer effect</td>
<td>Hepato cellular carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colon cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
</tr>
<tr>
<td><strong>Mumefural (BE extract)</strong></td>
<td>Anti-viral effect</td>
<td>Human influenza A virus (H1N1)</td>
</tr>
<tr>
<td><strong>BE (The water-soluble fraction)</strong></td>
<td>Stimulation of the proliferation and osteoblastic differentiation of cells</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td><em>Citric acid, malic acid, chlorogenic acid, 5-hydroxymethyl1-2-furfural (HMF)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oleanolic acid</strong></td>
<td>Anti-oxidantive effect</td>
<td>Sepsis and other fatal systemic inflammatory disorders</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory effect</td>
<td></td>
</tr>
<tr>
<td><strong>3.4 DHBA (Methanol extract)</strong></td>
<td>Anti-oxidative effect</td>
<td>Potential to treat and prevent Female infertility</td>
</tr>
<tr>
<td><strong>Citric acid malic acid</strong></td>
<td>Laxative effect</td>
<td>Constipation</td>
</tr>
<tr>
<td><strong>Acylated sucroses and acylated quinic acid (methanol extract)</strong></td>
<td>Anti-cancer effect</td>
<td>Melanogenesis</td>
</tr>
<tr>
<td><strong>Dried or pickled ume</strong></td>
<td>Anti-bacteria effect</td>
<td><em>Helicobacter pylori</em></td>
</tr>
<tr>
<td></td>
<td>Improvement of digestive dysmotility symptoms</td>
<td>GERD symptoms</td>
</tr>
<tr>
<td><strong>Fermented ume with probiotics</strong></td>
<td>Anti-inflammatory effect</td>
<td>Atopic dermatitis</td>
</tr>
</tbody>
</table>
### Phenolic acids and flavonoids

<table>
<thead>
<tr>
<th>Substance</th>
<th>Immune-enhancing effect</th>
<th>B. bronchiseptica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous extract including citric acid, malic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid picric acid</td>
<td>Anti-microbial effect</td>
<td>S. mutans biofilm, S. mitis, S. sanguis, P. gingivalis</td>
</tr>
<tr>
<td>Ethanol extract</td>
<td>Anti-cancer effect</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Flavonoid</td>
<td>Amelioration of glucose intolerance and fat accumulation</td>
<td>Anti-diabetic</td>
</tr>
<tr>
<td>Methanol extract</td>
<td>Hypouricemic effect</td>
<td>Anti-gout</td>
</tr>
<tr>
<td>Ume and LES (mixture)</td>
<td>Improvement of energy, lipid and glucose metabolism</td>
<td>Menopause</td>
</tr>
<tr>
<td>Ume, disodium succinate and span (mixture)</td>
<td>Memory-improving effect</td>
<td>Spatial memory, Working memory, Learning ability</td>
</tr>
<tr>
<td></td>
<td>Anti-depressant effect</td>
<td></td>
</tr>
</tbody>
</table>

### Description of Sponsorship

As for sponsorship, seven studies had government funding, six had private company sponsors, four had educational institute funding, three had government funding and private company sponsors, four had no sponsors and one had co-sponsorship of a province and educational institute. Of the articles from Japan, six had private company sponsors, three had government funding, three had government funding and private company sponsors, and three had no sponsors. Of the articles from Korea, four had government funding, three had educational institute funding and one had no sponsors. Of articles from China, two had funding from the dental association, one had educational institute funding and one had co-sponsorship of a province and educational institute.
Discussion

The purpose of this chapter is to interpret the results of this study. This study was conducted to systematically review the health benefits of ume and BE. In this chapter, I discuss the connection between the results and the literature. A discussion of unexpected discoveries follows. Next, this chapter describes implications of this project for holistic health, education, and future research. Finally, this discussion ends with a summary and concluding remarks.

Findings Supported by the Literature

The literature review covers the following health benefits: anti-cancer, anti-inflammatory, anti-oxidative, antimicrobial and antibacterial, and blood fluidity effects, as well as inhibitory effects on the pandemic influenza A (H1N1) virus. Ume also improves energy metabolism, treats Helicobacter pylori (Hp), improves stomach ulcers related to stress, improves diabetes, protects the cardiovascular system, and prevents osteoporosis. In addition, ume treats infertility, offers laxative effects, is a chemotherapeutic agent and anti-gout agent, and inhibits development of atopic dermatitis and melanogenesis. Finally, ume alleviates exercise-induced fatigue. However, no one has compared and contrasted the literature by conducting a systematic review.

Researchers of the 27 quality empirical studies selected in the systematic review confirm many of the above health benefits. Six research groups report anti-cancer effects (Hoshino et al., 2013; Matsushita et al., 2010; Mori et al., 2007; Nakagawa et al., 2007; Park et al., 2011; Tada et al., 2012). Next, four research groups support anti-microbial (Chen et al., 2011; Morimoto-Yamashita et al., 2011; Senevirante 2011; Wong et al., 2010). Three research groups address Anti-oxidative effects (Kawahara et al., 2009; Kono et al., 2014; Lee et al., 2013). Similarly, three research groups report anti-inflammatory effects (Hokari et al., 2012; Jung et al., 2010a; Kawahara et al., 2009). Finally, two research groups, which are Yingsakmongkon et al. (2008)
and Sriwilaijaroen et al. (2011), support anti-influenza virus effects. As far as the rest of the articles concerned, each research group reports per one health benefit.

However, certain health benefits were not found using the following pairs of keyword search terms:

1. “prunus mume” and “medicine or treatment” not “horticulture”
2. “concentrated prunus mume juice” and “medicine or treatment” not “horticulture”.

These health benefits include improving blood fluidity, improving stomach ulcers related to stress, and alleviating exercise-induced fatigue, as well as improving symptoms of gastrointestinal dysmotility associated with gastroesophageal reflux disease. Multiple key search terms could find more health benefits; however, there was not enough time for a solo researcher to conduct more searches and systematically review more articles.
Unexpected Findings

I presumed that some of the research articles would be from the U.S.; however, all 27 included studies came from Japan, China and Korea. These three countries have practiced oriental medicine for thousands of years and have a long history of utilizing ume as food as well as medicine. As a result, researchers from Japan, China and Korea may use traditional medicine, such as Kampo, Traditional Chinese Medicine and Traditional Korean Medicine and experience the health benefits of ume.

Most of the studies were conducted on a unique traditional method of processing ume. In Japan, scientists used BE extract which is a folk remedy in Japan, and this result was predictable since I searched with key terms. In China, scientists used aqueous extract methods, part of traditional Chinese medicine. In Korea, scientists used fermented ume, mixed with other herbs, and aqueous extract for their experiments. In particular, the fermentation technique of ume is a very unique method that was developed in Korea. According to Cha et al. (2007), locally grown natural herbs are used as medicine; epidemics and diseases differ with geography and environment, and the observation of differences in illnesses clearly stands out in such places as Korea, Japan and China. These countries built their own geographical, cultural and linguistic environments. Concerning this point of view, each country’s unique ume processing methods indicate that all three countries, which are geographically close together, share ume as a medicine. However, their methods for processing ume as medicine have developed individually in order to meet each country’s needs.

Another unexpected finding is that some Japanese research institutes are affiliated with private companies. On the other hand, no institutes in China and Korea have private sponsors. It is hard to know whether or not sponsors had an influence on positive results.
Finally, another unanticipated discovery is that some of the human cells used in in vitro studies were purchased from the US. This could indicate that the health benefits of ume are not limited to people from East Asian countries.

Implications

This section presents implications for future research and implication for holistic health.

Implications for Future Research. The results of my systematic literature review lead me to believe that it is possible to draw reliable conclusions from the available data to scientifically verify ume’s many possible health benefits. A few clinical studies have already been conducted, and some other studies are very close to clinical trials and could be conducted in the near future. For example, Zeniya who is one of the authors of Efficacy of MK615 for the Treatment of Patients with Liver Disorders (2012) is preparing for a clinical study. Mr. Suzuki, who is the contact author of In Vitro Inhibition of Human Influenza A Virus Infection by Fruit-Juice Concentrate of Japanese Plum (Prunus mume Sieb. et Zucc) (2008) and Mumeural and related HMF derivatives from Japanese apricot fruit juice concentrate show multiple inhibitory effects on pandemic influenza A (H1N1) virus (2011) continues to study the anti-viral effect of BE extract, mumefural, to be clinically proven new anti-influenza inhibitors. Morimoto-Yamashita et al. (2011) state in the literature, MK615 is safe to be used in mouth rinses, toothpaste and other oral products in the future. The literature and experts’ messages recognize ume’s great potential as an anti-cancer, an anti-microbial, an anti-oxidative, an anti-inflammatory and an anti-influenza agent, as well as many more agents. Further clinical studies are needed to show effectiveness of ume’s health benefits. Also, using multiracial cells in the lab tests could show the efficacy of health benefits of ume for all people worldwide.
For future research using systematic review of literature, a broader search with multiple key terms in a systematic review of literature could find more benefits of ume. In addition, communicating with authors in their native languages might maximize the chance of receiving detailed information about their latest research and findings.

**Implications for Holistic Health.** The holistic health community can play an important role in educating the public about the health benefits of ume and BE. Ume has a long history of being used as medicine and food. Scientific evidence now exists which supports the health benefits of this folk remedy.

Holistic health practitioners can utilize this knowledge to help their clients; for example, taking BE 3g/day for person weighs 55kg could prevent periodontitis, osteoporosis, and enhance anti-cancer effects (Matsumoto, 2000). Taking MK615 solution 13g/day improves liver disorders including hepatocellular carcinoma (Hoshino et al., 2013). In addition, eating umeboshi daily can prevent *Helicobacter pylori*-related chronic gastritis (Enomoto et al., 2010) and enhance symptoms of gastrointestinal dysmotility related to the gastroesophageal reflux disease (Maekita et al., 2015).

Furthermore, suggesting some recipes using BE or umeboshi, such as salad dressings, drinks and sushi will enhance clients’ quality of life as well. Holistic health practitioners should recommend clients who suffer serious diseases to consult with their primary doctors before taking ume products.

**Conclusion**

For thousands of years, in Japan, Korea and China, people have used ume for both medicinal and food purposes. In vitro studies, in vivo studies, and a few clinical studies have identified numerous health benefits. Scientists in Japan, Korea, and China continue to reveal
more medicinal uses of ume. In this systematic review of literature, ume was found to be
effective for improving more than 20 symptoms when observed in both lab tests and clinical
studies. In addition, ume could be effective for all people, regardless of race, since researchers
purchased some of the human cells used in in vitro studies from the U.S. and Japan. As a result
of this research project, my goals are to brings awareness to Western countries to promote the
health benefits of ume and BE and generate more research interest in the West and worldwide.
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A SYSTEMATIC REVIEW OF UME HEALTH BENEFITS


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bainiku-ekisu, a concentrate of prunus mume juice, on helicobacter pylori infection in humans. *Helicobacter, 11*(6), 589-591. doi: 10.111/j.1523-5378.2006.00463x

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A SYSTEMATIC REVIEW OF UME HEALTH BENEFITS


はじめまして。私、クリステンセン美奈と申します。現在、セントキャサリン大学の大学院で、ホリスティックヘルスを勉強しています。卒論のテーマに選んだのが、梅の効能についてで、Systematic review of literature のメソッドを使って、梅の効能について書かれた論文を読み、どれだけの効能があるのか調べているところです。先生の研究グループが執筆された” In Vitro Inhibition of Human Influenza A Virus Infection by Fruit-Juice Concentrate of Japanese Plum (Prunus mume Sieb. et Zucc)”を読ませていただきました。その後、先生たちのグループは、新しい論文を発表されていますか、また、何か新たな発見がありましたか？

もし、差支えなければ、教えていただけると幸いです。 5月に学内で、研究発表をする予定です。

どうぞ、よろしくお願いいたします。

クリステンセン 美奈
Appendix B

Example of the Message in English

To Whom It May Concern:

Hello, I am a graduate student at St. Catherine University under the supervision of Carol Geisler Ph.D., a faculty member in Holistic Health Studies. I am conducting a systematic review of literature in concerning the health benefits of Prunus mume. I read the study "Fermented Maesil (prunus mume) with probiotics inhibits development of atopic dermitis-like skin lesions in NC/Nga mice" that your group conducted in 2010. I would like to know if you have any new studies published after this study or any new findings.

Thank you for your assistance.

Sincerely,

Mina Christensen
Appendix

C-Example of Korean Translation

To 관계자분들께.

안녕하십니까, 저는 Carol Geisler 박사님 지도아래 St. Catherine 대학교를 졸업한 전체론적 건강학 연구 교수진입니다.

저는 Prunus Mume (매실나무)의 건강상 이점들에 관한 문학의 체계적인 분석을 위해 조사하고 있습니다.

2010년도에 시행된 여러분의 연구에 관해 '발효된매실' Prunus Mume(매실주)와 피부아토피 발달을 억제하는 생균제 - 아토피가 발현된 쥐(Nc/NGA)에 관해 읽어습니다.

2010년 이후로 새롭게 발표된 연구가 있는지, 아니면 새롭게 발견된 정보가 있는지에 관하여 알고싶습니다.

감사드립니다.

Mina Christensen
Appendix D

Example of Chinese Translation

你好，我是美国明尼苏达圣凯琳大学研究生，我的导师叫 Carol Geisler。她主要从事于医学健康方面研究。我最近正在系统研究樱桃露对身体健康的益处。我读了你们研究组 2011 年的研究报告“中国中草药对普通细菌抑制 (Antimicrobial activity of Chinese medicine herbs against common bacteria in biofilm. A pilot study)”非常想知道这个研究之后，你们是否出版了新的研究成果。

Mina Christenen
### Appendix E

**Characteristics of Included Studies and Characteristic of Excluded Studies**

**Table 4**

**Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Title</th>
<th>Title</th>
<th>Objective</th>
<th>Materials/Methods</th>
<th>Results</th>
<th>Country</th>
<th>Sponsorship</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chen 2011</td>
<td>The antimicrobial efficacy of Fructus mume extract on orthodontic bracket: A monospecies-biofilm model study in vitro</td>
<td>To examine antimicrobial effect of aqueous extract ume on the planktonic <em>Streptococcus mutans</em> (<em>S. mutans</em>).</td>
<td>Aqueous extract ume In vitro</td>
<td>An antimicrobial effect on <em>S. mutans</em> biofilm on orthodontic brackets.</td>
<td>China</td>
<td>2008 Innovation in Oral Care Awards (International Association for Dental Research/GlaxoSmithKline)</td>
</tr>
<tr>
<td>2</td>
<td>Enomoto 2010</td>
<td>Inhibitory effects of Japanese apricot (Prunus mume Siebold et Zucc.; Ume) on <em>Helicobacter pylori</em>-related chronic gastritis</td>
<td>To examine the correlation between ume intake and <em>Helicobacter pylori</em>-related chronic astrophic gastritis (CAG).</td>
<td>Dried or pickled ume Clinical (cohort study)</td>
<td>A preventive effect on CAG by inhibiting <em>H. pylori</em> infection and reducing active mucosal inflammation.</td>
<td>Japan</td>
<td>Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare of Japan</td>
</tr>
<tr>
<td>3</td>
<td>Hokari 2012</td>
<td>Efficacy of MK615 for the treatment of patients with liver disorders</td>
<td>To investigate hepatoprotective effects of MK615 in an animal model, and its clinical therapeutic effect.</td>
<td>MK615 (BE extract) In vivo (rats) and clinical</td>
<td>MK615 contains triterpenoids; including ursolic acid (UA), oleanolic acid (OA), lupeol, α-amyrin and β-sitosterol (anti-inflammatory and antioxidative action). MK615 protected hepatocytes from D-GalN-induced cytotoxicity in rats. MK615 also decreased elevated ALT and AST levels in patients with liver disorders. MK615 is promising hepatoprotective agents for patients with liver disorders.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td><strong>Hoshino 2013</strong> (Full Text)</td>
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</tr>
<tr>
<td><strong>Title</strong></td>
<td>Advanced hepatocellular carcinoma responds to MK615, a compound extract from the Japanese apricot “Prunus mume”</td>
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<tr>
<td><strong>Objective</strong></td>
<td>To investigate the effectiveness of MK615 against advanced Hepatocellular Carcinoma.</td>
<td></td>
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</tr>
</tbody>
</table>
| **Materials/Methods** | MK615 (BE extract)  
Clinical: Six patients with stage IV hepatocellular carcinoma (HCC) received MK615 (6.5g was administered twice per day) for more than three months as a final alternative therapy. |
| **Results** | The overall survival was 4.8 mo from the start. One patient has survived for more than 17 mo after administering MK615 and was in good condition at her latest follow-up examination in August 2013.  
Studies indicated that MK615 has anti-tumor effects against HCC in vivo. |
| **Country** | Japan |
| **Sponsorship** | MK615 was provided by AdaBio Co Ltd. (Takasaki, Japan) |

<table>
<thead>
<tr>
<th>Study 5</th>
<th><strong>Jung 2010</strong> (Full Text)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Fermented Maesil (Prunus mume) with probiotics inhibits development of atopic dermatitis-like skin lesion in NC/Nga mice</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To examine whether a fermented by-product of ume could suppress development of atopic dermatitish (AD)-like skin lesions in NC/Nga mice, a suitable model for AD in humans and canines.</td>
</tr>
</tbody>
</table>
| **Materials/Methods** | Fermented ume (FU) with probiotics  
In vivo (mice) |
| **Results** | Some component(s) of fermented ume has the ability to suppress the development of AD-like skin lesions in NC/Nga mice, probably via the induction of IL-10 or suppression of T cell or macrophage responses. |
| **Country** | Korea |
| **Sponsorship** | The Regional Technology Innovation Program of the Ministry of Commerce, Industry and Energy, Republic of Korea (grant No. RT105-01-01) and a CNU specialization Grant from Chonnam National University |

<table>
<thead>
<tr>
<th>Study 6</th>
<th><strong>Jung 2010</strong> (Full Text)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Immune-Enhancing Effect of Fermented Maesil (Prunus mume Siebold &amp; Zucc.) with Probiotics against Bordetella bronchiseptica in Mice.</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To examine Immune-enhancing effects of fermented ume with probiotics against Bordetella bronchiseptica in mice.</td>
</tr>
</tbody>
</table>
| **Materials/Methods** | Fermented ume with probiotics  
In vivo (mice) |
| **Results** | Fermented ume with probiotics enhances immune activity in mice, especially against B. bronchiseptica, via the potent stimulation of non-specific immune responses. |
| **Country** | Korea |
### Study 7  
**Kawahara 2009** (Full Text)

<table>
<thead>
<tr>
<th>Sponsorship</th>
<th>Korea Association of Industry, Academy and Research Institute through the Academic-industrial common technology development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Mechanism of HMGB1 release inhibition from RAW264.7 cells by oleanolic acid in <em>Prunus mume Sieb. Et Zucc.</em></td>
</tr>
<tr>
<td>Objective</td>
<td>To examine the mechanism of high mobility group box-1 protein (HMGB1) release inhibition from RAW264.7 cells by oleanolic acid in ume.</td>
</tr>
<tr>
<td>Materials/Methods</td>
<td>Fractionation of ume extract (F1, F2, F3 and F4): Ume extract was concentrated and dried and fractionated. Oleanolic acid (OA) [one of the triterpenoid from extraction of ume] In vitro (RAW 264.7 cells were obtained from USA).</td>
</tr>
<tr>
<td>Results</td>
<td>Ume extract and oleanolic acid inhibit HMGB1 release from stimulated RAW 264.7 cells via the Nrf2/HO-1 pathway and thereby play major roles in the regulation of cell survival in endotoxemia and other inflammatory conditions.</td>
</tr>
<tr>
<td>Country</td>
<td>Japan</td>
</tr>
<tr>
<td>Sponsorship</td>
<td>Ministry of Education, Culture, Sports, Science and Technology of Japan by grant-in-aid no. 19791618 (Y.M.) by grant-in-aid no. 17100007 (S.T.), and by a Health and Labour Science Research Grant from the Ministry of Health, Labour and Welfare (I.M.)</td>
</tr>
</tbody>
</table>

### Study 8  
**Kim 2008** (Full Text)

<table>
<thead>
<tr>
<th>Sponsorship</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>Memory-improving effect of formulation-MSS by activation of hippocampal MAPK/ERK signaling pathway in rat.</td>
</tr>
<tr>
<td>Objective</td>
<td>To investigate a molecular signal transduction mechanism of ume concentrated mixture on the behaviors of spatial learning and memory.</td>
</tr>
<tr>
<td>Materials/Methods</td>
<td>Ume concentrate mixtures: ume concentrate, disodium succinate and span80 (3.6: 4.6: 1 ratio) In vivo (rats)</td>
</tr>
<tr>
<td>Results</td>
<td>Daily administered ume concentrate mixture, disodium succinate and Span80 (3.6: 4.6: 1 ratio) (460 mg/kg day, p.o.) into the normal rats for 3 weeks showed improved memory and learning ability and enhanced anti-depressant effects.</td>
</tr>
<tr>
<td>Country</td>
<td>Korea</td>
</tr>
</tbody>
</table>

### Study 9  
**Ko 2013** (Full Text)

<table>
<thead>
<tr>
<th>Sponsorship</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td><em>Prunus mume</em> and <em>Lithospermum erythrorhizon</em> Extracts Synergistically Prevent Visceral Adiposity by Improving Energy Metabolism through Potentiating Hypothalamic Leptin and Insulin Signalling in Ovariectomized Rats</td>
</tr>
<tr>
<td>Objective</td>
<td>To investigate the antiobesity and hypoglycemic properties of ume and <em>lithospermum erythrorhizon sieb. Et Zucc</em> (LES) extracts in ovariectomized (OVX) rats with impaired energy and glucose homeostasis.</td>
</tr>
<tr>
<td>Materials/Methods</td>
<td>Ume extract and LES In vivo (overiectomized rats)</td>
</tr>
<tr>
<td>Results</td>
<td>Ume extract and LES treatment in overiectomized (OVX) rats normalized fat accumulation by decreasing food intake and increasing energy expenditure</td>
</tr>
</tbody>
</table>
through potentiating hypothalamic insulin signaling and restoring normal glucose and lipid metabolism. Therefore, ume extract and LES may be useful for alleviating metabolic dysregulation in post-menopausal women.

<table>
<thead>
<tr>
<th>Country</th>
<th>Korea</th>
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<tbody>
<tr>
<td>Sponsorship</td>
<td>Grant from the Korea Institute of Oriental Medicine (Grant no. K12080)</td>
</tr>
</tbody>
</table>

**Study 10**  
**Kono 2014** (Full Text)

<table>
<thead>
<tr>
<th>Title</th>
<th>3,4-Dihydroxybenzaldehyde Derived from <em>Prunus mume</em> Seed Inhibits Oxidative Stress and Enhances Secretion in Human Ovarian Granulosa Tumor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To investigate an effective bioactive compound derived from ume seed extract inhibits oxidative stress and enhances estradiol secretion in human ovarian granulosa tumor cells.</td>
</tr>
<tr>
<td>Materials/Methods</td>
<td>3,4-Dihydroxybenzaldehyde (DHBA) (compound from methanol extract ume seeds) In vitro [human ovarian granulosa tumor cell lines (COV 434) were obtained from Japan]</td>
</tr>
<tr>
<td>Results</td>
<td>3,4-Dihydroxybenzaldehyde (DHBA) protects granulosa cells from oxidative stress-induced apoptosis and enhances estrogen secretion via increased SF-1 expression. 3,4-DHAB may also contribute to the formation of good quality oocytes by activating granulosa cells. These functions of 3,4-DHBA may be effective for infertility treatment.</td>
</tr>
<tr>
<td>Country</td>
<td>Japan</td>
</tr>
<tr>
<td>Sponsorship</td>
<td>Ume was gift from Okayama Farm Co., Ltd. (Wakayama, Japan)</td>
</tr>
</tbody>
</table>

**Study 11**  
**Kono 2011** (Full Text)

<table>
<thead>
<tr>
<th>Title</th>
<th>A Prunus mume Extract Stimulated the Proliferation and Differentiation of Osteoblastic MC3T3-E1 Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To investigate the effect of ume extract on the proliferation and osteoblastic differentiation in pre-osteoblastic MC3T3-E1 cells.</td>
</tr>
<tr>
<td>Materials/Methods</td>
<td>The water-soluble fraction of ume (UWF) from Bainiku Ekisu (BE): Major components: citric acid, malic acid, chlorogenic acid and 5-hydroxymethyl-2-furfural. In vitro (MC3T3-E1 cells were obtained in Japan)</td>
</tr>
<tr>
<td>Results</td>
<td>UWF increased the alkaline phosphatase (ALP) activity, cell proliferation and mineralization. The gene expression of osteopontin and bone morphogenetic protein-2, which are markers in the early period of osteoblastic differentiation, were significantly enhanced by the water-soluble fraction of ume. The water-soluble fraction of ume therefore stimulated the proliferation and osteoblastic differentiation of cells and may have potential to prevent osteoporosis.</td>
</tr>
<tr>
<td>Country</td>
<td>Japan</td>
</tr>
<tr>
<td>Sponsorship</td>
<td>None</td>
</tr>
<tr>
<td>Study 12</td>
<td>Lee 2013 (Full Text)</td>
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<tr>
<td><strong>Title</strong></td>
<td>Fermented Prunus Mume with Probiotics Inhibits 7,12-dimethylbenz[a]anthracene and 12-O-Tetradecanoyl phorbol-13-acetate Induced Skin Carcinogenesis through Alleviation of Oxidative Stress</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the inhibitory effect of fermented ume with probiotics against 7, 12-dimethylbenz[a]anthracene (DMBA), 12-o-tetradecanoyl phorbol 13-acetate (TPA)-induced skin carcinogenesis in mice via its antioxidative potential.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>Fermented ume with probiotics Phenolic compounds: phenolic acids and flavonoids In vivo (mice)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Fermented ume has the ability to suppress the development of DMBA-TPA induced skin carcinogenesis, via the reduction of lipid peroxidation, enhancing total antioxidant capacity and phase II detoxifying enzymes.</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Korea</td>
</tr>
<tr>
<td><strong>Sponsorship</strong></td>
<td>National Research Foundation of Korea grant No-2009-0071504, funded by the Korean government</td>
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<thead>
<tr>
<th>Study 13</th>
<th>Matsushita 2010 (Full Text)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Advanced malignant melanoma responds to Prunus mume Sieb. Et Zucc (Ume) extract: Case report and in vitro study</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the effectiveness of MK615 by treating a patient with advanced malignant melanoma (MM), and also to investigate the mechanisms underlying the effect of MK615 using the human MM cell line SK-MEL28.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>MK615 (BE extract) Triterpenoids Clinical-67-year-old Japanese woman with metastasis of malignant melanoma on her left thigh administered MK615 for 5 months to evaluate metastatic lesions. In vitro (Human SK-MEL28 melanoma)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>MK615 decreased the expression of RAGE in SK-MEL28 cells. Moreover, it significantly suppressed the release of HMGB1 by SK-MEL28 cells. The results suggest that MK615 inhibits cell migration and invasion. MK615 was effective in a patient with advanced malignant melanoma.</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Sponsorship</strong></td>
<td>Research grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, by Grants-in-Aid 21390483 (to K.K.) MK615 were provided by AdaBio Co. Ltd (Takasaki, Japan)</td>
</tr>
</tbody>
</table>
### Study 14

**Title**
New anti-proliferative agent, MK615, from Japanese apricot “*Prunus mume*” induces striking autophagy in colon cancer cells *in vitro*

**Objective**
To investigate the anti-neoplastic effect of MK615, an extract from the ume extract against colon cancer cells.

**Materials/Methods**
MK615 (BE extract)
In vitro (cancer cell lines, SW480, COLO, and WiDr were purchased from USA. Sex and race of cells were varied)

**Results**
MK615 has an anti-neoplastic effect against colon cancer cells. The effect may be exerted by induction of apoptosis and autophagy.

**Country**
Japan

**Sponsorship**
MK615 was provided by the Japan Apricot Co. (Gunma, Japan)

### Study 15

**Title**
MK615: A new therapeutic approach for the treatment of oral disease

**Objective**
To investigate the antimicrobial activities of MK615 against a range of oral bacterial pathogens.

**Materials/Methods**
MK615 (BE extract)
Invitro (*Streptococcus mutans*)

**Results**
MK615 had an inhibitory effect against growth of oral bacteria and formation of *S. mutans* biofilm.

**Country**
Japan

**Sponsorship**
Grants-in Aid for Scientific Research (2279094 and 21390483) from the Ministry of Education, Culture, Sports, Science and Technology of Japan
MK615 was a gift from Ada Bio (Gunma, Japan)

### Study 16

**Title**
The laxative effects of Maesil (*Prunus mume* Siebold & Zucc.) on constipation included by a low-fibre diet in a rat model

**Objective**
To investigate effectiveness of ume in promoting the frequency of defecation and contraction of the rat colon.

**Materials/Methods**
Aqueous extract of ripened ume (RU) and unripened ume (UU)
Citric acid and malic acid were evaluated.
In vivo (rats)
In vitro (rats’ colon)

**Results**
Ume extract, citric acid and malic acid, were effective in promoting the frequency of defecation and contraction of the rat colon, which provided scientific basis to support the use of ume as a potential therapeutic in treating constipation.

**Country**
Korea

**Sponsorship**
Gwangyang City and Jeollanamdo Institute of Natural Resources Research (JINR) Core-Competence Program grants to S. Kim.
### Study 17  
**Title**  
New Antineoplastic Agent, MK615, from UME (a Variety of) Japanese Apricot Inhibits Growth of Breast Cancer Cells in vitro

**Objective**  
To investigate the antineoplastic effects of MK615 against breast cancer cells.

**Materials/Methods**  
- MK615 (BE extract)  
- In vitro (breast cancer cell lines, MDA-MB-468 and MCF7 were purchased from USA)

**Results**  
MK615 effectively inhibits the growth of breast cancer cells in vitro, possibly by cell cycle modification and apoptosis induction. MK615 should be further investigated as a promising anti-breast cancer agent.

**Country**  
Japan

**Sponsorship**  
MK615 was provided by Japan Apricot Co., Ltd. (Gunma, Japan)

### Study 18  
**Title**  
Acylated sucroses and acylated quinic acids analogs from the flower buds of *Prunus mume* and their inhibitory effect on melanogenesis

**Objective**  
To investigate inhibitory effect of isolated compounds, acylated sucroses and acylated quinic acids analogs on melanogenesis in theophylline stimulated B16 melanoma 4A5 cells.

**Materials/Methods**  
- Methanolic extract from the flower buds of ume  
- A cylated quinic acids  
  - Invitro (five acylated quinic sucroses and three acylated quinic acids, Murine B16 melanoma 4A5 cells)

**Results**  
Acylated quinic acid analogs substantially inhibited melanogenesis. Acylated quinic acid analogs are promising therapeutic agents for the treatment of skin cancers.

**Country**  
Japan

**Sponsorship**  
Ministry of Education, culture, Sports, Science and Technology (MEXT)-Supported Program for the Strategic Research Foundation at Private Universities, by a Grant-in Aid for Young Scientists from the Japan Society for the Promotion of Science (JSPS).
### Study 19

**Seneviratne 2011** (Full Text)

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Prunus mume extract exhibits antimicrobial activity against pathogenic oral bacteria</th>
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</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate antimicrobial properties of ume extract against oral pathogens related to dental caries and periodontal diseases.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>Ume extract (dried powder of ume was obtained commercially) In vitro (<em>Streptococcus mutans, S. sobrinus, S. mitis, S. sanguinis, Lactobacillus acidophilus, P. gingivalis, Aggregatibacter actinomycetemcomitans, and Candida</em>)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Organic acids are the main ingredient of ume and ume significantly inhibits all the bacterial species. Ume has an antibacterial effect against a wide range of oral pathogens. Ume extract may be a potential candidate for developing an oral antimicrobial agent to control or prevent dental diseases associated with oral pathogenic bacteria.</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>China</td>
</tr>
<tr>
<td><strong>Sponsorship</strong></td>
<td>2008 Innovation in Oral Care Awards (International Association for Dental Research/Glaxo SmithKline)</td>
</tr>
</tbody>
</table>

### Study 20

**Park 2011** (Full Text)

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Induction of apoptosis by ethanol extract of <em>Prunus mume</em> in U937 human leukemia cells through activation of caspases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the pro-apoptotic effects of ethanol extract of ume (EEU) in U937 human leukemia cells.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>Ethanol extract of ume (EEU) In vitro (U937 human leukemia cells were obtained from USA)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>EEU may be a potential chemotherapeutic agent for use in the control of human leukemia U937 cells and that further studies are needed for the identification of the active compounds.</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Korea</td>
</tr>
<tr>
<td><strong>Sponsorship</strong></td>
<td>Supported by the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Education, Science and Technology (2010-0001730), and Technology Development Program for Agriculture and Forestry (610003-03-1-SU000), Ministry for Food, Agriculture, Forestry and Fisheries.</td>
</tr>
</tbody>
</table>

### Study 21

**Tada 2012** (Full Text)

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>MK615, a <em>Prunus mume</em> Steb. Et Zucc (‘Ume’) Extract, Attenuates the Growth of A375 Melanoma Cells by Inhibiting the ERK1/2-Id-1 Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the anticancer effects of MK615 in association with Id-1 and related protein kinases in the A375 melanoma cell line.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>MK615 (an extract of compounds from BE) In vitro (A375 melanoma cells were obtained from USA)</td>
</tr>
</tbody>
</table>

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MK615 plays a major role in regulating the death of A375 cells. MK615 is a potential therapeutic agent for treating malignant melanoma.

**Results**

**Country**
Japan

**Sponsorship**

MK615 used in this study was provided by AdaBio (Takasaki, Gumma, Japan).

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### Study 22

#### Shin 2013 (Full Text)

**Title**
Ethanol extract of the *Prunus mume* fruits stimulates glucose uptake by regulating PPAR-γ in C2C12 myotubes and ameliorates glucose intolerance and fat accumulation in mice fed a high-fat diet.

**Objective**
To examine whether a 70% ethanol extract of ume (EEU) exhibits anti-diabetic effects.

**Materials/Methods**
- Ethanol extract of ume (EEU)
- In vitro (C2C12 and HEK293 cells were purchased from USA)
- In vivo (mice)

**Results**
EEU, which contains flavonoids, is a potential functional food for the prevention and treatment of diabetes and obesity, due to its ability to maintain glucose metabolism by regulating PPAR-γ activation and suppressing fat accumulation.

**Country**
Korea

**Sponsorship**
“Food Functionality Evaluation program” under the Ministry of Food, Agriculture, Forestry and Fisheries, and Korea Food Research Institute, Republic of Korea

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### Study 23

#### Wong 2010 (Full Text)

**Title**
Antimicrobial activity of Chinese medicine herbs against common bacteria in oral biofilm. A pilot study

**Objective**
To investigate the antimicrobial activity of some TCM’s including ume that have been used to treat symptoms related to infection (e.g. fever, inflammation, cough) on several bacteria found in the oral biofilm to identify potential agents to control oral infection and diseases.

**Materials/Methods**
- Aqueous extract 20 traditional Chinese medicines extract including ume
- In vitro (S. mitis, S. sanguis, S. mutans and P. gingivalis were cultured)

**Results**
Ume had inhibitory effects on *S. mitis, S. sanguis, S. mutans* and *P. gingivalis* in vitro.

Acids including citric acid, malic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid picric acid might create a low pH environment that may account for its antibacterial effect.

**Country**
China

**Sponsorship**
University Research Grant no.: 10207346.15633.08003.323.01, the University of Hong Kong
<table>
<thead>
<tr>
<th>Study 24</th>
<th>Yi 2012 (Full Text)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Hypouricemic effect of the methanol extract from <em>Prunus mume</em> fruit in mice</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To verify a possible hypouricemic effect of methanol extract from ume in mice with potassium oxonate-induced hyperuremia.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>Methanol extract ume. The solutions were combined, filtered, and concentrated under reduced pressure and lyophilized into powders (MUF)</td>
</tr>
<tr>
<td><strong>In vivo (mice)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>The results indicated that the beneficial hypouricaemic effect of MUF may be mediated at least in part, by inhibiting XO activity in the liver. The study suggests that ume and its extract may have a considerable potential for development as an anti-gout agent for clinical application.</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>China</td>
</tr>
<tr>
<td><strong>Sponsorship</strong></td>
<td>The project was co-financed by the Natural Science Foundation of Fujian Province of China (No. 2011J05081) and Huaqiao University (No. 09BS507) to Li-Tao Yi (L.T.Yi).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 25</th>
<th>Yingsakmongkon 2008 (Full Text)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td><em>In Vitro</em> Inhibition of Human Influenza A Virus Infection by Fruit-Juice Concentrate of Japanese Plum (<em>Prunus mume</em> Sieb. Et Zucc)</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the ability of BE to inhibit human influenza A virus infection.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>Bainiku Ekisu (BE) with phosphate buffered saline (PBS) followed by filtration with membrane filter. In vitro (viruses: A/PR/8/34 (H1N1), A/Aichi/2/68 (H3N2), A/Memphis/1/71 (H3N2) cells: Mardin-Darby canine kidney [MDCK])</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>The present study has demonstrated that BE can inhibit human influenza A virus infection of host MDCK cells, presumably by activity of a heat-stable lectin-like molecule(s).</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Sponsorship</strong></td>
<td>The sialidase inhibitor, zanamivir, was a gift from Glaxo Co., Ltd.</td>
</tr>
<tr>
<td>Study 26</td>
<td>Sriwilaijaroen 2011 Full Text</td>
</tr>
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<tr>
<td><strong>Title</strong></td>
<td>Mumeferul and related HMF derivatives from Japanese apricot fruit juice concentrate show multiple inhibitory effects on pandemic influenza A (H1N1) virus</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To investigate the most effective compound of BE extract against pandemic influenza A (H1N1) virus.</td>
</tr>
<tr>
<td><strong>Materials/Methods</strong></td>
<td>BE extract was diluted with water, centrifuged and eluted, then separated by analytical high-performance liquid chromatography (HPLC). Five compounds were isolated: HMF, MF, MF', MA1 and MA2. In vitro (Mardin-Darby canine kidney (MDCK) cells and A/Narita/1/2009 (H1N1)), gene of human α-2,6-sialyltransferase (SIAT-1)</td>
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<tr>
<td><strong>Results</strong></td>
<td>MF possesses multiple activities including lectin-like, anti-HA (inhibition of viral attachment) and anti sialidase (blockage of the release of viral ribonucleoprotein into the host cytoplasm and virions to new host cells) activities contributing to its anti-influenza activity in cell culture. MF may be taken to reduce influenza infection and may be useful as a molecular seed for development of novel anti-influenza inhibitors.</td>
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<tr>
<td><strong>Country</strong></td>
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<tr>
<td><strong>Sponsorship</strong></td>
<td>Nakano BC Co. Ltd., Wakayama, Japan</td>
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<tr>
<th>Study 27</th>
<th>Maekita 2015 (Full Text)</th>
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<tr>
<td><strong>Title</strong></td>
<td>Japanese apricot improves symptoms of gastrointestinal dysmotility associated with gastroesophageal reflux disease</td>
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<tr>
<td><strong>Objective</strong></td>
<td>To investigate the effectiveness of ume consumption on gastroesophageal reflux disease (GERD)-related symptoms.</td>
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<tr>
<td><strong>Materials/Methods</strong></td>
<td>Dried and pickled ume Clinical (Questionnaires)</td>
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<tr>
<td><strong>Results</strong></td>
<td>Daily ume intake may improve dysmotility symptoms, resulting in relief of GERD symptoms. The effect is more obvious in non-elderly and H. pylori-negative subjects.</td>
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Table 5

*Characteristics of Excluded Studies*

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<th>Study</th>
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<td>Jung 2010</td>
<td>Multiple herbs were utilized and it was hard to single out the effect of ume.</td>
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<td>Lee 2011</td>
<td>Multiple herbal combinations make it difficult to identify the benefits of ume alone.</td>
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<td>Nakajima 2006</td>
<td>This study was not able to successfully eradicate <em>H. pylori</em> in humans using 130mL of a 1% solution of BE. The study should include 2% or higher solution of BE for comparison.</td>
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<td>Takemura 2014</td>
<td>No significant effect of Umezu Polyphenols on Blood Pressure was observed. They have 8 participants in the placebo group and 7 participants in the polyphenol group. They need a larger sample.</td>
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<td>Zhang 2009</td>
<td>Multiple herbs were combined and it was hard to identify the effect of ume.</td>
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Appendix F

Quality Assessments of Included Studies Based

Table 6

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X yes (item adequately addressed); NA not applicable

### Quality Assessments of Included Studies Based

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