A Product Proposal

Berry Balm Medicinal Shrub

Superior Diabetic Wellness Support

Halebee

A hale and holistic approach to diabetes

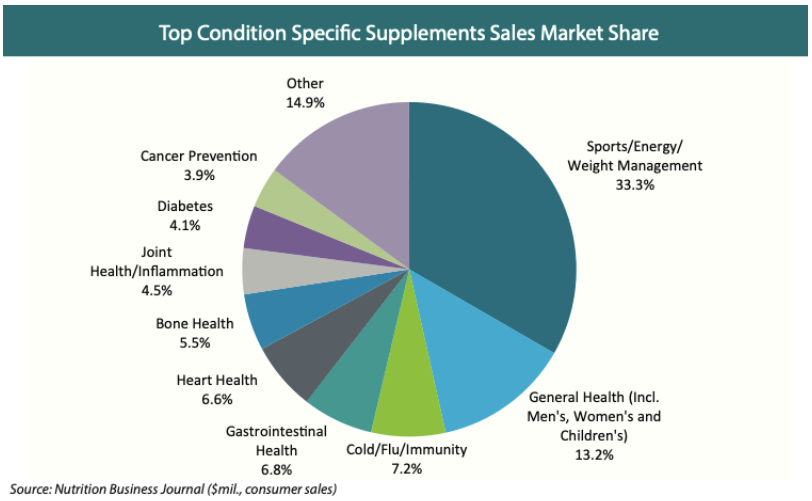
Table of Contents

Innovate

Founded in 2018, Halebee.com has provided counseling, education, and support for clients living with Type 2 Diabetes Mellitus (T2DM). As part of our growing services, we are developing new product offerings. Halebee.com takes a holistic approach to providing clients the information they need to make positive life choices. Dietary choices are at the forefront of that effort and from the outset, we wanted to make a wellness formula with apple cider vinegar (ACV) for its wonderful and natural antidiabetic effects! On its own, ACV has been shown to help stabilize blood sugar and post-prandial blood glucose spikes (Seok & Cha, 2012; Siddiqui et al., 2018). The antidiabetic benefit makes it the perfect delivery method for our herbal tonic for clients with diabetes. We have developed our **diabetic wellness product concept** with a deep understanding of traditional development approaches. Our formulation is grounded in quality, published, peer-reviewed research. This product proposal outlines our concept, formulation, and manufacturing considerations.

Target Market

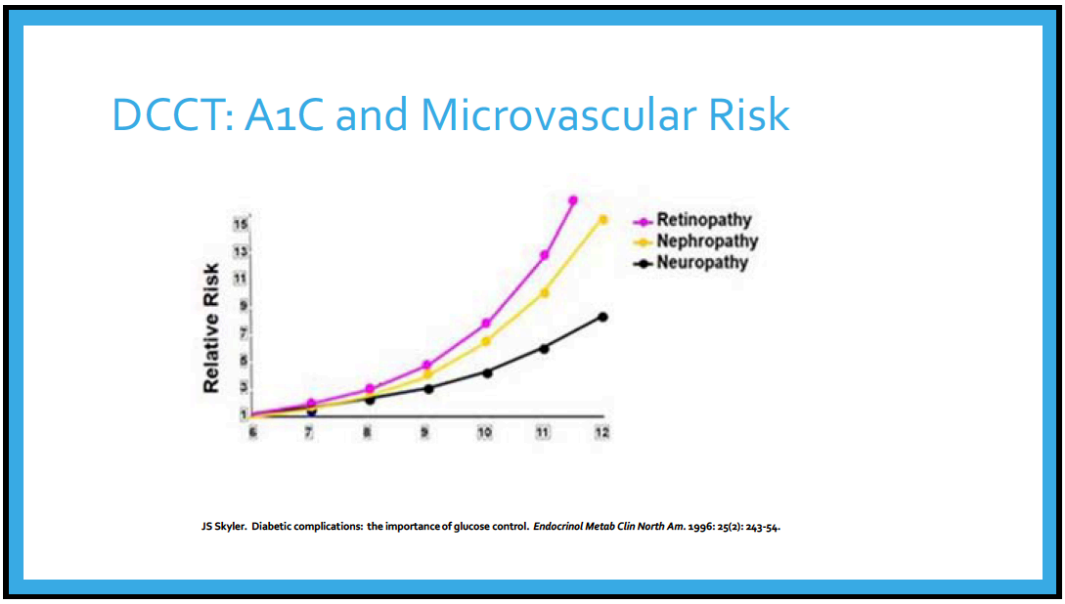
9.5% of Americans have diabetes and an estimated 33.9% of U.S. adults have prediabetes(CDC 2018), which adds up to over 114.4M people living with chronic diabetes symptoms. These staggering facts come with a slew of health complications including, but not limited to: depression, blindness, kidney failure, heart disease, stroke, limb amputation, skin issues, dental disease, diabetic neuropathy, and pregnancy complications (Rowley et al., 2017). The estimated medical costs and lost work and wages for people diagnosed with diabetes totaled over $245B in 2014 (National Diabetes Statistics Report, 2014). These ever-growing numbers have fueled diabetes-related drug, device, food, and supplement development as companies are keen to take advantage of the enormous market. The diabetes supplement market is growing steadily along with the growing number of patients. Research shows that diabetes supplements represent 4.1% of the total supplement market; which is currently valued at over $151.9B in 2021.



Sports, Energy, and Weight Management supplements continue to hold the largest market share of condition categories, up from 29.8% in 2017 and driven by increasing consumer use of protein for weight management and everyday performance. The 14.9% of market share attributed to Other conditions includes 13 conditions listed in the following chart.

Product Concept

We have decided on formulating a product to support wellness and resilience in clients living with the neuropathy associated with T2DM. To that end, we have identified a number of goals to achieve with this formula detailed below. First and foremost, our formulation should support wellness-based resilience and encourage stress-reduction in clients with T2DM. After years of raised blood glucose levels, the relative microvascular risk increases as patients $A1_C$ level increases (see chart below). Neuropathic pain is a common symptom for long-term T2DM patients and it will be ideal for our wellness formula to have supportive secondary benefits. Third, we also need a wellness formula that will not further raise blood glucose levels and may provide antidiabetic and antiglycemic effects. Fourth, patients living with T2DM often experience depression after diagnosis, which can be compounded by pain from diabetic neuropathy. Our wellness formula should support antidepressant effects if possible. Lastly, it's important that our formula be easy to consume, as people managing long-term chronic illnesses are likely dealing with the additional stress of taking many oral or injectable medicines already.



Adaptogenic tonics

Adaptogens are a relatively new category of herb medicine from the last 50 years. They are mild in effect and can exhibit stimulating effects. Adaptogenic herbs can be further divided into primary and secondary adaptogens. Primary adaptogens have their primary effect as stress normalizing. An Introduction to Herbal Medicine by Miles Drake (n.d., p. 1) describes how adaptogens work to "help the body adapt to stress and support or restore normal levels of life force or energy; such a plant is often called a 'tonic', and often work by enhancing adrenal gland function."

Adaptogens contain triterpenoid and phenolic constituents, especially phenylpropanoids, which are known for their stress reducing effects. Examples of adaptogens include *Panax ginseng*, *Rhodiola rosea* and *Schizandra sinensis*. Some top reasons for using adaptogens in a clinical setting are to promote vitality & disease resistance; reduce stress, depression & anxiety; support chronic illness & convalescence. Stress increases hormones in the body, such as cortisol, which adaptogens help to normalize. Given our formula goals laid out earlier, we have decided to investigate the following adaptogenic plants , secondary herbs, and CBD dominant chemovar in our formulation:

Formulation Condition	Formulation Plant
Wellness based resilience	Ashwagandha (*Withania somnifera*)
Adaptogenic, neuroprotective	Schisandra (*Schisandra chinensis*)
Antidepressant, adaptogenic	St. John's Wort (*Hypericum perforatum*)
Adaptogenic, antidiabetic effect	American ginseng (*Panax quinquefolia*)
Neuropathic pain	Sativa-based CBD (*Cannabis sativa*)
Antidiabetic, hypoglycemic	Apple cider vinegar
Antidiabetic, hypoglycemic	Bilberry (*Vaccinium myrtillus*)

Reflection on our choices

Depression

T2DM patients experience high rates of depression. Depression can be induced by the realities of living with a chronic illness, negative side effects of medication, general poor health, and required dietary change (Semenkovich, Brown, Svrakic, & Lustman, 2015). Diabetic neuropathy in the limbs can also be a side effect of long-term high blood glucose levels. Neuropathic pain is often accompanied by depression, which can compound depression already experienced by those living with T2DM. A formula that addresses this issue would be ideal, so we initially considered including St. John's Wort in our formula for its secondary antidepressant effects. However, hypericum found St. John's Wort is known to speed up the metabolism of medicine, which would not be suitable for diabetics taking medicine to control their blood sugar levels. Other concerns are a very small number of case studies which demonstrated that Ginseng and St. John's Wort independently lead to mania (Joshi & Faubion, 2005). Although the risk is small, taking them together could compound the effect. To eliminate these risks, we have decided to remove St. John's Wort from our formula.

Synergy

In Rasoanaivo et al. (2011), the researchers present a paper describing how synergistic interactions of whole plant or combined crude plant constituents may provide a stronger benefit than single compound extracts. They begin this narrative review, by defining pharmacodynamic synergy as multiple phytochemicals working in concert to improve their effect. An example of this synergy can be found in the antimalarial effects of *Artemisia annua* which appear to be greater than the compound artemisinin alone. Another example is the pharmacodynamic synergy between turmeric curcumin and black pepper piperine, whereby the piperine can enhance the absorption of curcumin in the digestive system, thereby increasing its effect on the body. The biggest potential is for the synergy in our formula is the ginseng and schisandra – which are two parts of the TCM Shengmai San (also with *Ophiopogon japonicus*) recipe. These herbs used together can target oxidative stress, diabetes, and lipedema and coronary issues.

Traditional development approaches

A traditional approach to herbal medicine asks us to evaluate a client's imbalance and build a formula that strengthens their weaknesses and supports their metabolism rather than treating their acute concerns (Moore n.d.). By bringing the body back into hormesis, acute problems may be changed or disappear. This approach prompted me to learn the mechanisms of Type 2 Diabetes and to understand its associated metabolic imbalances. In his book Principles and Practices of Constitutional Physiology for Herbalists, Moore describes the philosophies of both Traditional Chinese Medicine (TCM) and Ayurveda are to "strengthen the person and then treat their problem" (p. 7). His therapeutic approach is analogous, whereby western herbalists should evaluate and diagnose the imbalances before treating acute symptoms.

Traditional Western Medicine

In his traditional approach to organ system evaluation, Moore looks for signs of excess or deficiency in the greater organ of the body. Patients with T2DM can experience many

symptoms of liver imbalance; specifically, deficiency, including unstable blood sugar, low energy, and obesity. It is a condition acquired later in life and may be associated with heavy alcohol intake. According to Moore (n.d), herbs used to treat liver deficiencies will also stimulate the other organs that specialize in metabolism, including the pancreas. *Schisandra chinesnis* and *Ginseng* spp. are both used in liver deficiencies and will make good options for our formula.

Traditional Chine Medicine

In older TCM Diabetes or Xiao-ke is considered a thirsting or wasting syndrome, with excessive heat and drying, and effecting the lungs, stomach, and kidneys. The main factors attributed to Diabetes were improper diet, emotional disturbances, and a Yin deficiency (Covington 2001). However, the recent explosion of Type 2 Diabetes Mellitus (T2DM) has caused TCM practitioners to rethink this categorization. A review by Guo et al. (2014) took a second look at syndrome differentiation under new TCM guidance. They explicitly identify different stages of the syndrome and associated symptoms linked directly to the stages of T2DM and the functions of insulin. This differentiation allows the TCM practitioner to select different herbs depending on the stage of the syndrome and stage of diabetes. The table on page 8 demonstrates the stages of diabetes, key indicators, symptoms, and TCM herbs commonly used in treatment.

We want our wellness formula to have a secondary effect on diabetic neuropathy, which is a late stage T2DM complication, therefore we are particularly interested in the TCM herbs at the far-right end of the below table; where we are excited to see that *Schisandra chinesnis* and *Ginseng* spp. appear on above list of herbs, as they are two adaptogens that we have discussed earlier in this proposal. This gives us more confidence in our selection choices.

Ayurvedic approaches

In the Ayurveda medicinal system, T2DM can be classified as a “sweet urine” disease, which is attributed to an imbalance or excess of Kapha dosha. However, obesity can be caused by an imbalance in the Vata dosha. “When people with Vata imbalances overeat to soothe themselves, Kapha can in turn become imbalanced and, over time, contribute to the development of type 2 diabetes” (Patel, 2012, p. 2). Herbs used to treat an imbalance both Vata dosha and excess of Kapha dosha include: *Gymnemna sylvestre*, fenugreek, cinnamon, turmeric, and bilberry. From among these herbs, I have found a secondary herb for my formulation: bilberry.

Table 1. TCM Diabetes Syndrome Differentiation

Herbs used	Xiao Chaihu: Bupleurum, Scutellaria baicalensis, Pinellia ternata, and **Ginseng sp***p*.	Da Chaihu: Bupleurum, Chinese rhubarb, Scutellaria baicalensis, Citrus aurantium, Radix Paeoniae Rubra	Xiao Xianxiong: Rhizoma coptidis, Pinellia ternata, Snakegourd seed	Shangmai San: Ophiopogon japonicas, **Schisandra chinensis**, **Ginseng spp**,	QijuDihuangWan Chinese wolfberry, Chrysanthemum, Chinese yam, and Cornus officinalis, Rehmannia dried root, Chinese yam, Fructus Corni, Cassia twig, and Monkshood
Key indicators	Higher fasting plasma glucose, postprandial blood sugar, and glycosylated hemoglobin		Increased triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL), and decreased high density lipoprotein (HDL)		The levels of blood specific viscosity, fibrinogen, hematocrit, erythrocyte sedimentation rate (ESR)
Symptoms	Liver depression, emotional distress, depression	Emotional and digestive symptoms	Abdominal obesity, chest suppression, intestinal dampness	Lack of strength, shortness of breath, spontaneous, night sweats, upset, palpitations, insomnia	Urinary and nocturia frequency, blurred vision, dizziness, tinnitus
TCM Syndrome	Qi stagnation	Liver and stomach heat stagnation	Phlegm and heat stasis	Dual deficiency Qi and Yin	Dual deficiency Yin and Yang
Stage	Prediabetes	Early T2DM	Middle T2DM	Late T2DM	T2DM Complications

T2DM Progression

Formulation

Apple cider vinegar

Having settled on ACV as delivery method, we investigated different formats of delivery. Daily intake of ACV of between 15-30 mL per day [1-2T] (Samad, Azlan, & Ismail, 2016; Seok & Cha, 2012; Siddiqui et al., 2018) is one standard dosage so we needed to be able to comfortably serve at least that much in a single dosage. We initially investigated developing cinnamon vinegar gummy bears by making a sample batch. They were easy to make, but it was challenging figuring out how to get the rest of the herbs into the liquid required for dosage and to make something that was edible and tasty. After experimentation, we switched out the cinnamon for the bilberry to make the taste more palatable. We also discovered that a person would need to consume more than a snack pack size of gummies to get the required dosage – so we next investigated making a vinegar shrub. This seems to be best way to blend all of the ingredients into a palatable formula that can easily be added to plain or bubbly water for a tasty and medicinal beverage to drink. We will extract the bilberries and the schisandra berries directly in the vinegar to help retain their color in the formula and to better retain the flavonoids, ligans, and tannins found in those berries.

Dosage form, posology and data on safe use.

In her Immortelle paper, Peterson (2015) describes how different extraction processes produces different constituents from the same plant. For example, essential oil distillation produces monoterpenes, sesquiterpenes, monotepenenoids, and phenolic compounds whereas alcohol extraction processes produce alkaloids, carotenes, flavonoids, and tannins. Determining the best extraction process for each herb requires the knowledge of the output of the process and of the constituents you are trying to extract. Details of our investigations for our primary herbs are below.

American ginseng

We started researching the posology and formula dosages for adaptogen American Ginseng (*Panax quinquefolium*). Ginseng in TCM is commonly used in capsule or granular (freeze dried) form, but Michael Moore believed that the tincture format (1:7; 70% alcohol) is morally best and most bioavailable (Moore 1995). The EU Ginseng monograph lists either a dry extract with ethanol (3-7:1; 40%) or a liquid extract (1:1; 30% ethanol) as the recommended dosage. According to Braun & Cohen (2015, p. 439) different parts of the plant contain different concentrations of the ginsenosides so they recommend “elucidation from clinical tries as to the dosage range of therapeutics is required”. Hoffman (2003, p. 570) suggests that the “common daily dosage used in clinical trials is 200mg (1:5 extract)” or a daily dose of 1-2g of root material.

Sativa

Although Mucke et al. (2018) found that “there is no **high-quality evidence** for the efficacy of any cannabis-based product” for treating chronic neuropathic pain, they did find that cannabis-based medicines increase the number of people finding pain relief 30% compared to placebo(p. 2). The best studies they reviewed included the use both aerosolized, inhaled sprays and

tinctures. We found that sativa compositions which include similar THC and CBD levels may provide results better than THC alone (Comelli et al., 2010). The CBD constituents work in synergy with THC constituents to better support pain relief . Research has shown that formulations at low dosages preformed equally well as high-dosage ones (Wallace et al., 2015). Based the above research we have settled on a formation that includes a sativa-based cannabis chemovar in a low dosage tincture, similar to a product like Spasm Relief™. We are going to include an extract that contains 5mg of THC and 5mg of CBD in our formula.

Table 2. Formula Herbs Daily Dosage and Posology

Herb	**Formula Extract (concent., % AV)**	**Dosage**	**Citations**
American Ginseng	3mL (1:5 70%)	200mg 1:5 70%	Moore 1995; Braun & Cohen 2015; Hoffman 2003
Schisandra	10 berries 2:1 (vinegar:fruit)	500mg	Harnischfeger and Tewocht 1994; Thompson 2021
Ashwagandha	3 mL	250mg	Salve, Pate, Debnath, & Langade 2019
Sativa	3mL	5mg THC & 5mg CBD (1:5 50%)	Portnoy et al. 2012; Comelli et al. 2009; Uberall 2020
Bilberry	1/4C berries 2:1 (vinegar:fruit)	9g – 150g ligans, tannin	Habanova et al 2016
Vinegar	30mL	N/A	Seok & Cha, 2012; Siddiqui et al., 2018

Extraction and blending methods.

We started this recipe working backwards from 16oz (473mL) bottles. We are settled on using 2T (29.6 mL) as the serving size – mixed with a cup of water to prepare a berry beverage. This would allow 1 bottle to last up to 2 weeks. Using 2T as the servicing size, we estimated the amount of extracts that need to be included in our formula.

The goal of extraction is to use a solvent to pull out the primary and secondary metabolites of the herbs that we are using. Each herb contains a mix of different constituents which may be more favorably extracted by different solvents. We investigated the constituents of the primary herbs in our herbal formula to determine the best extraction method before blending. We set upon a procedure for extracting and blending the ingredients that is detailed below.

American ginseng

Active compounds of American ginseng are ginsenosides and saponins of the glycosides group that are abundant in roots, leaves, stem, and fruits of the plant. Ginsenosides are suggested to be primarily responsible for health benefits on the nervous system (Braun & Cohen 2015; Szczuka et al. 2019). Since the EMA monographs provide data for both alcoholic and liquid extractions – both our options for us. For our formula, we have settled on using an alcoholic

process to best express those ginsenosides. We can test for a standard 200mg dosage of ginsenosides to make sure our extraction process is working as expected.

Ashwagandha

Constituents traditionally extracted from Ashwagandha root include alkaloids, flavanol glycosides, sterols and phenolics. Previous studies have shown that the extracted and purified components of Ashwaganda (Withanone, Withanolide A) “are active when used at low dose and protect the glial and neuronal cells from oxidative stress” (Kaul et al. 2016, p. 2). This new research by published by Kaul et al. (2016) set out to explore the bioactivity in Ashwagandha leaves for the reasons:

1. to obtain ample supply without sacrificing the plants,
2. to rule out soil contaminants,
3. as an easy distinction of the healthy versus diseased plants,
4. to ease of cleaning and extraction processes, and
5. to avoid strong unpleasant odor of roots.

They demonstrated that both alcoholic and water extracts of Ashwagandha leaves contain active constituents including Withanolides, Withanone and Withaferin A. They suggest using Withaferin A and Withanone as standards for testing the extraction. We can test for these constituents when we build our own formula.

Schisandra

We will be using the berries of schisandra, which contain the following active constituents: lignans (schizandrin, schisandrols, schisantherins, deoxyschizandrin, gomisin), triterpenes, phytosterols, stigmasterol, organic acids (citric and malice acids), volatile oil, vitamins A, C and E, minerals (phosphorous, manganese, silicon), tannins, resin, sitosterol, saccharides, and pectin (Thompson, 2021). The berries are typically used in a decoction or infusion. We will be extracting these in vinegar to preserve the color in the formula.

Batch mixing and blending

Quality variation in herbal formulas can be caused by differences in raw materials that differ by region, climate, and time of harvest. Fluctuation in production processes is another source of variation and batch mixing has been developed to smooth out those differences. Batch mixing “can reduce the impact of variations in raw materials and the fluctuation in operations on the quality of the final drug product” (Yan & Qu, 2013). Batches of formula are mixed using a well-designed proportion “to get a mixture in which the contents of the important constituents are closer to the reference standard” (Yan & Qu, 2013). If possible, we will follow a formula for batch mixing developed by Yan and Qu which seeks to use the minimum number of batches of extracts and reduce waste.

As we started to build our formula, we had difficulty creating a test batch that had the dosage amounts in our recommended serving size of 2T. We had to rethink our extraction and blending process to get our formula to a correct serving size. We have settled on water + alcohol extraction as the method of extraction for root materials in this formula. The bilberry will be

extracted in a heated apple cider vinegar solution. The other herbal extractions will be added to the apple cider vinegar+bilberry+schisandra liquid to create the shrub.

Ingredient stability testing

The WHO recommends that stability data be supplied on the product with an expiration date on the package (Kumadoh & Ofori-Kwakye, 2017). Vinegar is a liquid solution and one of the most typical pickling agents with 5%-10% acetic acid and it preserves food by altering water activity or pH (Valshali, Jhandai, Jadhav, & Gupta, 2019). With a PH level of around 4.6, it inhibits bacteria from growing and provides a preservative effect. This wonderful preservative should give our shrub a stable shelf life of up to 24 months!

Testing on the final formula will begin with testing for the PH level of the product to make sure that it is at least 4.6pH. As I am planning on water extraction of the herbal constituents, I will follow Criteria A of microbial tests suggested in Kumadoh & Ofori-Kwakye, 2017 (see table below).

Table 3. Acceptance criteria for microbial tests

PH Level	4.6
Total aerobic microbial count	< $5x10^7$ CFU / g
Total yeast and mold count	< $5x10^5$ CFU / g
Bile tolerant Gram negative bacteria	< 10^2CFU / g
Salmonella spp.	Absent in 10mL
Escherichia coli	Absent in 1mL

This product will be sold in the United States, which is temperate climate zone II. The product should be shelf stable at 78.8°F with an average humidity of 65 (Kumadoh & Ofori-Kwakye, 2017). The testing should be conducted in the container the product will be sold in – in this case I will be selecting a glass bottle that can be stored in a pantry shelf or a refrigerator. The main stability tests will be to determine that the vinegar shrub maintains its PH level over time.

Adulteration testing

In a chemical analysis of Sheng Mai San produced by five different commercial pharmaceutical products, researchers tested methods to compare the variability and composition of the products (Cheng & Tsai, 2018). They successfully used both high-performance liquid chromatography tandem (HP-TLC) mass spectrometry and physical examination by electron and light microscopes to detect differences compared to a solution prepared in house. To create the in-house test solution, *Panax ginseng* (30.0 g), *Radix ophiopogonis* (30.0 g) and *Fructus schisandrae* (15.0 g) were mixed together and extracted with 700 mL of boiling water for 30 min. The decoction was filtered, and the solution was evaporated under vacuum (Cheng & Tsai, 2016). The in-house solution was then compared to the commercial products to identify any adulteration of the commercial products. Adulteration is a problem in the supplements industry, so we settled on following similar testing procedures to allow us to test the quality of our product pre- and post-production.

The product will go through 3 rounds of testing:

1. Initial base materials tests (HP-TLC fingerprinting specific to formula)
2. Batch test for the product
3. Random product test

Small batch testing will be conducting using a company named Alkemist. The testing will be completed according to AHPA for prepared products. Test between 10 mL of each batch less than 50,000mL. Test samples will be sent to Eurofins Scientific Inc. Audit program: if pre-ship sample and the final lot for 3 shipments matches supplier Certificate of Analysis, then we will only test pre-ship sample on subsequent lots.

Manufacturing

New Ingredient Procurement

Ingredients will be procured from reputable sources practicing harvesting methods that follow sustainability guidelines. Our initial procurement procedure will involve purchasing extractions from vendors such as Mountain Rose Herbs. While buying extracts from established companies such as this will increase the price of production, it will allow us to reduce the risk associated with buying products from cowboy outfits outside of the USA.

Batch Manufacturing Process

The bilberry and schisandra berries will be extracted in ACV at room temperature for 21 days. Each batch will be tested for a minimum of ligan constituents expected. Then each extract will be batch tested individually before blending. Blending will be completed using a formula developed for minimizing waste in the blending process. The final product will be tested a final time for the makeup of components and to verify the batch mixing process is working.

Labeling

INTERNAL
50% THC/50% CBD Mild Psychoactive
High Healing Value

Ingredients:
Apple Cider Vinegar, Bilberry(Vaccinium myrtillus), American ginseng(Panax quinquefolia), Schisandra(*Schisandra chinensis*) extract, Ashwagandha(*Withania somnifera*) extract, and Sativa(*Cannabis sativa*) extract.

Description:
ORGANIC PRODUCT. Berry Balm Shrub is a medicinal vinegar product that has shown to be effective for diabetic neuropathy pain relief. Temporarily soothes nerve pain symptoms. This adaptogenic tonic supports healthy endocrine and central nervous systems.

The Berry Balm Shrub contains about 45% v/v of alcohol i.e. up to 5mg per dose. The amount of alcohol in the maximum daily dose for most people (2T) is about the same as found in two

teaspoons of beer or about one teaspoon of wine. This product can be harmful for those suffering from alcoholism

Suggested Use:
SHAKE WELL. BEFORE USING. Add 2T to 8oz of water up to twice daily. **Store out of reach of children. Keep refrigerated after opening.**

Made in USA.

References

Braun, L., & Cohen, M. (2017). Herbs & natural supplements: An evidence-based guide, volume 2. Australia: Elsevier. Gardner, Z., & McGuffin, M. (Eds.). (2013).

Centers for Disease Control and Prevention (2018). Diabetes Report Card 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2018.

Cheng, Y. Y., & Tsai, T. H. (2016). Analysis of Sheng-Mai-San, a Ginseng-Containing Multiple Components Traditional Chinese Herbal Medicine Using Liquid Chromatography Tandem Mass Spectrometry and Physical Examination by Electron and Light Microscopies. *Molecules* (Basel, Switzerland), 21(9), 1159. https://doi.org/10.3390/molecules21091159

Comelli F, Bettoni I, Colleoni M, Giagnoni G, & Costa B. (2009) Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress. *Phytother Res*. 2009 Dec;23(12):1678-84. doi: 10.1002/ptr.2806. PMID: 19441010.

Covington, M. (2001) Traditional Chinese Medicine in the Treatment of Diabetes. *Diabetes Spectrum* 14:154-158.

Drake, M. (n.d.) An Introduction of Herbal Medicine. URL Accesses May 28, 2021. https://www.academia.edu/8069449/AN_INTRODUCTION_TO_HERBAL_MEDICINE_Miles

Guo, J., Chen, H., Song, J., Wang, J., Zhao, L., & Tong X. (2014) Syndrome Differenctiation of Diabetes by the Traditional Chinese Medicine According to Evidence-Based Medicine and Expert Consensus Opinion. *Evidence-based Complementary And Alternative Medicine* 2014:1-7

Joshi, K. G., & Faubion, M. D. (2005). Mania and Psychosis Associated with St. John's Wort and Ginseng. Psychiatry (Edgmont (Pa. : Township)), 2(9), 56–61.

Kaul, S. C., Ishida, Y., Tamura, K., Wada, T., Iitsuka, T., Garg, S., Kim, M., Gao, R., Nakai, S., Okamoto, Y., Terao, K., & Wadhwa, R. (2016). Novel Methods to Generate Active Ingredients-Enriched Ashwagandha Leaves and Extracts. PloS one, 11(12), e0166945. https://doi.org/10.1371/journal.pone.0166945

Kumadoh, D. and Ofori-Kwakye, K. (2016) Dosage forms of herbal medicinal products and their stability considerations - an overview (Links to an external site.). J Crit Rev. 4 (4): 1-8

Moore, M. (n.d.) *Principles and Practice of Constitutional Physiology for Herbalists*. Southwest School of Herbal Medicine. Albuquerque NM.

Moore, M. (1995) Herbal Materia Medica, 5th edition. Southwest School of Botanical Medicine, Albuquerque, NM.

National Diabetes Statistics Report (2014) Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services. Centers for Disease Control and Prevention.

Petersen, D. (2015) Immortelle Essential Oil and Extract: Are Two Preparations Better than One? *Journal of the American Herbalists Guild*. 13(1): 21-27.

Rasoanaivo, et al. (2011). Whole-plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions. (Links to an external site.) *Malaria journal*, 10 Suppl 1 S4. https://doi.org/10.1186/1475-2875-10-S1-S4 (Links to an external site.)

Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. (2017) Diabetes 2030: Insights from Yesterday, Today, and Future Trends. Popul Health Manag. 2017 Feb 1; 20(1): 6–12. Published online 2017 Feb 1. Last Accessed: July 1, 2021. Doi: 10.1089/pop.2015.0181

Salve, J., Pate, S., Debnath, K., & Langade, D. (2019). Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical Study. Cureus, 11(12), e6466. https://doi.org/10.7759/cureus.6466

Samad, A., Azlan, A., & Ismail, A. (2016) Therapeutic effects of vinegar: a review. *Current Opinion in Food Science*, 8: 56-61, ISSN 2214-7993, https://doi.org/10.1016/j.cofs.2016.03.001.

Semenkovich K, Brown ME, Svrakic DM, Lustman PJ.(2015) Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. Drugs. 2015 Apr;75(6):577-87. doi: 10.1007/s40265-015-0347-4. PMID: 25851098.

Seok, H., & Cha, B. S. (2012). Response: Balsamic Vinegar Improves High Fat-Induced Beta Cell Dysfunction via Beta Cell ABCA1 (Diabetes Metab J 2012;36:275-9). *Diabetes & Metabolism Journa*l 36(5), 390. doi:10.4093/dmj.2012.36.5.390

Siddiqui, F. J., Assam, P. N., de Souza, N. N., Sultana, R., Dalan, R., & Chan, E. S. (2018). Diabetes Control: Is Vinegar a Promising Candidate to Help Achieve Targets?. *Journal of Evidence-based Integrative Medicine*, 23, 2156587217753004. doi:10.1177/2156587217753004

Szczuka, D. Nowak, A., Zaklos-Szyda, M., Kochan, E, Szymanska, G., Motyl, I. & Blasiak J. (2019) American Ginseng (Panax quinquefolium L.) as a Source of Bioactive Phytochemicals with Pro-Health Properties. Nutrients 11:1041

Thompson, M. [blog] Schisandra monograph. URL Access July 2021. https://www.herbrally.com/monographs/schisandra

Wallace, M., Marcotte, T., Umlauf, A., Gouaux, B., & Atkinson, J.H. (2015) Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. *J Pain* July 2015 16(7): 616–627. doi:10.1016/j.jpain.2015.03.008.

Valshali, Jhandai, P., Jadhav, V. J., & Gupta, R. (2019). Bio-preservation of Foods: A Review. *European Journal of Nutrition & Food Safety*, 11(4), 164-174. https://doi.org/10.9734/ejnfs/2019/v11i430159

Yan, B. and Qu, H. (2013) An approach to optimize the batch mixing process for improving the quality consistency of the products made from traditional Chinese medicines *Journal of Zhejiang Univ-Sci B* (Biomed & Biotechnol) 2013 14(11):1041-1048