cornell iGEM

Synthetic Biology Project Team

URSOLIC ACID HANDBOOK

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Introduction

This year, Cornell iGEM will be addressing the problem of breast cancer with the project Oncurex. Our goal is the create a much more efficient and environmentally friendly method of producing Ursolic Acid (UA), a compound that is common place in many fruits and vegetables and have been implicated in potential anti-cancer treatment. Ursolic Acid has a storied history, finding its place in medicinal treatments since ancient times.

While the main focus of our project started with Ursolic Acid in relation to breast cancer, interviews with UA specialists highlighted the many other medicinal properties of UA. UA can be applied to anti-inflammatory diseases, anti-virals, anti-diabetes and even more! Learning of all these applications, we were inspired to continue researching and learning of all these medicinal properties. Oncurex, while focusing on cancer treatments, is not solely limited by this. We hope to highlight all the potential applications of ursolic acid beyond breast cancer.

It is also extremely important to focus on the main sources of Ursolic Acid. UA can be found in a wide variety of fruits and vegetables across the world. Given it's history in traditional medicines, Cornell iGEM found it apt to not only focus on just the medicinal properties, but also the sources of UA and the rich cultural diversity it has in countries across the globe.

This handbook is comprised of two components. The first part is an introduction into the cultural and medicinal uses of plants containing ursolic acid across the globe. We use key plants from each continent as case studies of the unique place ursolic acid has throughout history. The second part is an analysis of the wide range of applications in the medical field. While we chose to focus on breast cancer, this is one of many possible applications. We hope this hand book serves as a guide to not only understand the biological and physiological mechanisms behind UA, but also the rich cultural and historical context UA lives in.

Cultural & Medicinal Uses of Plants Containing Ursolic Acid

NORTH AMERICA

Cranberry (*vaccinium macrocarpon*)

Native American tribes have used cranberries for medicinal purposes for many years. They were utilized to treat wounds and infections because cranberries have natural antibacterial properties. They harvested cranberries from peaty bogs and marshes.

Today, cranberries continue to grow on vines in freshwater bogs, mainly in the northern United States and parts of southern California. They grow on vines close to the ground and the fruits go ripe in September and October.

Cranberries are so useful because they have cancer-fighting antioxidants that come from compounds that may lessen the radicals that can lead to heart diseases, diabetes, cancer, and other chronic conditions. Among these promising antioxidants are quercetin, myricetin, anthocyanins, proanthocyanidins, and **ursolic acid**. Furthermore, cranberries can help keep your mouth healthy by lessening the amount of acid in your mouth. They can also protect against liver disease, lower blood pressure, improve eyesight, improve cardiovascular health, help prevent UTIs, aid with digestion digestion, and improve gut health. Cranberries were such a helpful and healthy compound that when early European settlers came to the Americas, indigenous groups shared them to help prevent sailors from getting scurvy.

Beyond medicinal purposes, cranberries played an important role in some Native American cultures. In fact, the Aquinnah Wampanoags of Martha's Vineyard have a holiday called sasemineash, which translates to Cranberry day. Cranberries were eaten fresh, ground, or mashed with cornmeal and baked into bread. Additionally, they could be

mixed with wild game and felted fat to form pemmican – a survival ration for the winter months which lasted for months and was easily portable on long journeys.

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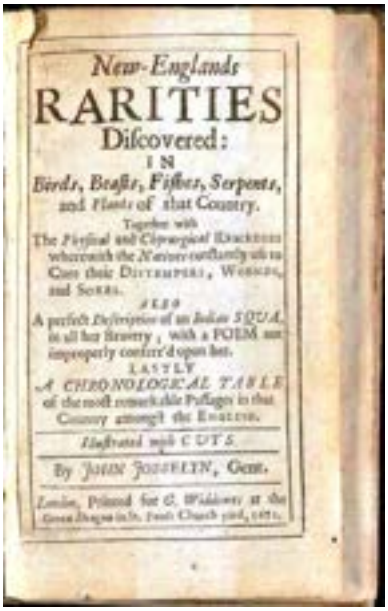
Blueberry (*vaccinium corymbosum*)

Blueberries have a long history of traditional use, as indigenous peoples of North America have long revered blueberries for both their medicinal uses and delicious flavor.

In terms of culinary uses, indigenous groups often cooked blueberries into sauces, mixed them with meat, or mixed them with cornmeal to create bread. Medicinally, blueberries were integral to Native American healing practices, as the benefits of blueberries include improving digestion, alleviating coughs and sore throats.


New-Englands
RARITIES
Discovered:
IN
Birds, Beasts, Fishes, Serpents,
and Plants of that Country.
By JOHN JOSSELYN, Gent.

Englishman John Josselyn, an observer of the 17th-century inhabitants of northern New England with a particular interest in medicinal uses of plants referred to “bill berries” (a close relative to the blueberries), as being used “to cool the heat of Feavers, and quench Thirst. They are very good to allay the burning heat of Feavers, and hot Agues [a fever that shakes the body], either in Syrup or Conserve”. This account highlights the many uses of blueberries in indigenous culture.

Today, blueberries are cultivated primarily in the temperate regions of North America, including the northern United

States and Canada. Blueberries grow best in acidic, sandy soils. Blueberry bushes produce berries that ripen in from July through September.

Modern research supports the significant health benefits of blueberries. Because they are rich in antioxidants such as anthocyanins, flavonoids, **ursolic acid**, and vitamins C and K, blueberries help prevent oxidative stress and inflammation. Furthermore, the compounds in blueberries can lower one's risk of chronic diseases such as heart disease, diabetes, and types of cancer. Blueberries have been found to support cognitive function, enhance memory, and promote healthy aging. Blueberries also promote good cardiovascular health because they regulate blood pressure and cholesterol levels. Finally, the high fiber content found in blueberries helps aid in digestive health.

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SOUTH AMERICA

Pacaya Palm (*Chamaedorea tepejilote*)

The pacaya palm plays an important role in Mesoamerican cultures, especially among Indigenous communities in Central America. It has many uses, especially pertaining to its edible shoots which can be harvested from the heart of the palm and are commonly known as "palm hearts".

Palm hearts are a prized ingredient in traditional cuisine and are featured in a variety of dishes such as salads, soups, stews, and stir-fries.

In addition to its culinary applications, the pacaya palm has significant medicinal value. Indigenous peoples use the pacaya palm to address a range of health issues like aiding in digestion and reducing inflammation. While these traditional uses are well-documented in indigenous practices, more scientific research is needed to fully understand and validate the medicinal properties of the pacaya palm.

Beyond its role in food and medicine, the pacaya palm is integral to local craftsmanship and daily life. Artisans weave the leaves of the pacaya palm into intricate baskets, mats, and other handcrafted goods. The pacaya palm is also featured frequently in local rituals and ceremonies because it represents a connection to the land and ancestral traditions. It is often included in ceremonies that honor the natural world or celebrate the changing seasons.

The pacaya palm mainly grows in the humid tropical regions of Central America. Due to their deep connection and respect for nature, indigenous communities practice careful management to ensure that the plant's ecosystem remains intact and that future generations can continue to benefit from its resources.

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EUROPE

Olives (*Olea europaea*)

Olives have been an integral part of the Mediterranean diet for thousands of years. Known for their distinctive taste and versatility in culinary applications, olives are not only a popular ingredient but also a powerhouse of health benefits.

One of the primary health benefits of olives comes from their containment of monounsaturated fats, particularly oleic acid. These healthy fats have extreme cardiovascular benefits as they reduce levels of LDL (bad) cholesterol while increasing HDL (good) cholesterol – a balance which is integral to reducing the risk of heart disease. Specifically, the consumption of olive oil, which is extracted from olives, has been extensively studied and shown to contribute to overall heart health.

Along with being packed with healthy fats, olives contain a wide variety of antioxidants. They are a significant source of vitamin E and polyphenols, compounds that play a vital role in combating oxidative stress and inflammation. Antioxidants are crucial for protecting cells from damage caused by free radicals, which can lead to chronic diseases and aging. Olives also contain significant amounts of Vitamin A (important for maintaining good vision and a healthy immune system), Vitamin K (vital for proper blood clotting and bone health), and B vitamins (involved in energy metabolism and red blood cell formation).

Additionally, olives have high fiber content, which supports regular bowel movements, prevents constipation, and contributes to a feeling of fullness that can help people reduce overall calorie intake. Furthermore, olives have been associated with a reduced risk of several chronic diseases. The anti-inflammatory and antioxidant properties of olives and olive oil have been linked to lower risks of conditions such as cancer and diabetes. These benefits are

attributed to the bioactive compounds such as **ursolic acid** found in olives, which help to mitigate inflammatory responses and improve overall health.

In both ancient Greece and Rome, olives played a critical role in both culinary practices and spiritual beliefs. Greeks and Romans utilized olive oil for sautéing, dressings, and as a base for many dishes, including salads, stews, and bread dips. Olive oil was often enhanced with herbs and spices to create various culinary delights and proved to be a very important commodity that they traded on the market, meaning it was also extremely important for the economy.

In Greece, olives were sacred to Athena and represented peace and victory. This peace and victory is symbolized by the olive branch used in religious ceremonies and as prizes in athletic competitions. Romans often offered olives to the gods and used olive oil in religious rituals.

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Calluna (*Ericacae*)

Calluna, commonly known as heather, has many health benefits and traditional uses. Heather is used in herbal medicine due to its anti-inflammatory and antimicrobial properties. Its soothing effects reduce inflammation and fight infections, helping to treat

respiratory conditions such as coughs and bronchitis. Additionally, heather is believed to be diuretic, meaning that it reduces fluid retention and supports urinary health. These benefits stem from the plant containing compounds such as flavonoids (plant pigments with antioxidant properties), tannins (polyphenolic compounds with astringent properties that can help in treating conditions such as diarrhea and sore throats), and saponins (compounds that help clear mucus form the respiratory tract and contribute to diuretic effects).

Beyond being extremely useful for its medical applications, heather plays a significant role in European cultural and folklore traditions. In Scotland, heather is celebrated as a symbol of admiration and protection and is often associated with good fortune and prosperity. It is used often in bouquets and decorations that are put on display at Scottish weddings. Similarly, heather symbolizes solitude and tranquility in Scandinavian countries.

Heather is commonly planted in gardens and landscapes. Heather is natural to Europe, Iceland, the Azores, and the Faroe Islands. However, it can also be found in Asia, North America, Greenland, Turkey, Madeira, and the mountains of northern Morocco. This is because it is commonly planted in gardens and used for decorative uses. The wood from the heather plant is often used to craft durable furniture. Also, the flower can be used to create floral arrangements because of its natural aesthetic appeal.

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Rosemary (*Rosmarinus officinalis*)

Rosemary is an aromatic evergreen shrub native to the Mediterranean region that has needle-like leaves and clusters of small, vibrant blue-violet flowers. Rosemary is prized for its distinctive, pine-like fragrance which enhances a variety of culinary dishes. Its robust, earthy taste makes it a versatile ingredient in many recipes such as being used to flavor roasted meats such as lamb, chicken, and pork. Rosemary is also traditionally used in stews and soups, or paired with roasted vegetables such as potatoes, carrots, and bell peppers. Finally, rosemary can also be found in many breads, marinades, and dressings – truly, it is an all-encompassing herb!

Beyond being an all-encompassing herb, rosemary has significant medicinal applications. Its essential oils are celebrated for their potent antioxidant, anti-inflammatory, and antimicrobial properties. Key compounds in rosemary include rosmarinic acid, which has been shown to have powerful anti-inflammatory and antioxidant effects; cineole, known for its potential to improve respiratory function and alleviate coughs; camphor, which can provide analgesic and anti-inflammatory benefits; and ursolic acid, also known for its anti-inflammatory benefits. These compounds work together

to support cognitive function, alleviate muscle pain, aid digestion, and promote respiratory health. Furthermore, the herb's invigorating aroma is often used in aromatherapy to enhance mental clarity and alleviate stress.

Culturally, rosemary holds a significant place in Mediterranean traditions and folklore because it has long been associated with remembrance and fidelity. This cultural significance is evident in its use in weddings and funerals. The herb's presence in ancient rituals and its continued relevance in contemporary practices underscore its timeless appeal and importance in human history.

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Lavender (*lavandula angustifolia*)

Lavender is native to the Mediterranean region, where it thrives in well-drained, sunny environments. The plant is known for its purple flowers and silvery-green foliage and sweet, floral aroma. Lavender is used widely for its scent, taste, and medicinal purposes.

In the kitchen, lavender can be used to add a unique, aromatic touch to a variety of dishes. It is often incorporated into baked goods like cookies, cakes, and scones, providing a delicate floral flavor. It is also paired well with coffee or complex cocktails, and lavender lattes have proved to be an extremely trendy summer flavor in 2024. Lavender also pairs well with savory dishes such as roasted chicken or lamb.

Also, lavender has great cultural significance. It has been widely respected in Mediterranean traditions for both its fragrant aroma and natural aesthetic. It has symbolic associations with purity, calm, and devotion, which is shown because it often appears in religious ceremonies and weddings. Historically, lavender was also a favorite ingredient in the herbal baths of both Greeks and Romans, and was even considered an herb of love. In fact, it was

believed that a sprinkle of lavender water on the heat of a loved one would keep the wearer chaste. The Greek naturalist, Dioscorides, praised the medicinal attributes of lavender in the first century A.D., and in ancient Egypt it was used both a perfume and an essential ingredient for incense. Lavender was thrown all over castle floors and in sickrooms as both disinfectant and deodorant. Furthermore, it was used as an ingredient smelling salts and as a disinfectant in wartime. Lavender was also used to embalm corpses, tame lions and tigers, repel mosquitos, and even was added to a variety of special lacquers and varnishes.

Lavender is valued because of its multiple medicinal uses. Traditionally, lavender was used to treat headache, hysteria, and nervous palpitations, hoarseness, palsy, toothaches, sore joints, apoplexy, colic, coughs, and poor digestive systems. Currently, lavender is likely most well-known for its use as an essential oil, where it is renowned for its calming and relaxing effects. It is an extremely popular choice in aromatherapy to reduce anxiety and improve sleep quality. Many people rub lavender around their face to help promote a good sleep. Key compounds in lavender oil include linalool and linalyl acetate, which contribute to its sedative and anti-anxiety effects. Additionally, ursolic acid helps contribute to the anti-inflammatory properties of lavender, which along with its antiseptic properties make it useful for soothing minor burns, insect bites, and skin irritations. Finally, lavender tea is often used to aid digestion and relieve headaches.

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Asia

Loquat *(Eriobotrya Japonica)*

The loquat is a fruit rich in Ursolic Acid that grows native to southeast China. It is commonly found in the mountains, where a variety of loquats was able to blossom for more than a thousand years. The fruit is known for it's tangy and sweet flavor similar to mangos and other citrus fruits.

Historically, while the loquat is native to China, it was introduced to Japan as a main stay, being developed horticulturally as a prized cultural fruit. Within both China and Japan, the loquat is deep soaked in mythology. In China, the fruit represents prosperity. It's beautiful fruit was considered the source of many dragon's origins, so only Chinese royalty was able to eat the fruit. This reverence carried over to Japan, where the loquat became a symbol of longevity and beauty, and was the subject of many such poems that illustrated the beauty and bounty of nature.

Loquats have many medicinal properties, and is considered one of the most prominent fruits in traditional medicine. Both the fruits and leaves have been used to treat a variety of illnesses, including a very early start to cancer treatments in folk history. It is extensively discussed in one of the first medicinal books ever published, the Compendium of Materia Medica in 1578. Very high in nutrients and compounds such as ursolic acid, it's extract has been used to target many organs in the body. Currently, the loquat is known to contain many beneficial plant compounds. It is rich in phenols, triterpenes, sugars, vitamins and other minerals that provide physiological benefits to those that consume them.

As such, loquats have treated illnesses across the body. It's leaf has been used to treat respiratory illnesses such as cough, bronchitis and asthma through drinking the tea. Ingesting the fruit itself which is high in ursolic acid helps treat inflammation, cellular damage, congestion, lowering hypertension and a wide variety of other applicable treatments Eating many loquats as well can create a sedative effect as well. It was mostly absorbed through ingestion. Loquat tea, it's flesh in jams and jelly, and even syrups have all been touted as traditional medicine designed by nature to be a healer.

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Java Plum *(Syzygium Cumini)*

The Java plum is a fruit common to the Indian subcontinent that is fast growing and relatively common place. It's leaves grow from pink to dark green, and the fruit develops from a green hue when unrip to a deep crimson and black when ripe. The fruit is considered sweet and sour, creating a deep flavor that draws many followers in.

In traditional medicine, the Java Plum has largely been used as an ornamental fruit that is both delicious and nutritious. In particular, the tree has been revered by Buddhists who considered it a sacred piece of nature. It was seen particularly as one of the blessed plants of Lord

Krishna, making the Java Plum highly revered as a “fruit of the Gods” and planted near many Hindu temples as a result. It has been imported to many other countries, including Uganda and many states in the US. Because it grows so rapidly, it has been deemed an invasive plant particularly in the US.

The Java Plum is so useful because it holds many medicinal properties as a source of nutrients and vitamins such as ursolic acid. It holds many antioxidant activities, allowing it to reduce inflammation from cell damage. Beyond this, the Java plum aids in immunity, gastrointestinal distress and blood sugar regulation. In particular, the Java Plum has undergone many studies due to it’s anti-diabetic and hyperlipidemic effects as well, giving it huge potential for medicinal treatments.

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Africa:

Oregano *(Origanum Vulgare)*

Oregano is a common spice found around the mediterranean area, including parts of North Africa. The plant is commonly called the “beauty of the mountain” due to it’s location and it’s beautiful blooms. It grows best in locations with dry soil and full sun, making it much more common around the equator. There are a wide variety of species that each contain a different flavor. The different profiles of oregano make it a culinary staple in many kitchens. Used in a wide variety of dishes, it provides a deeper more complex flavor that can elevate stews, dips, pizza and other foods.

Culturally, oregano has a vast history. It has been used not only for medicinal purposes, but also for other more symbolic methods of healing. Many spells and potions cite oregano as a provider of happiness, justice, protection, and love. Indeed, it is very commonplace at traditional celebrations as well.

During ancient times, many believed oregano could be used as an anti-poison agent. Grinding up the oregano would allow people to rub it onto their wounds like a paste, leading to supposed anti-bacterial and anti-inflammatory properties. In turn, many believed this would help with muscle and joint pain, including soreness and arthritis. Additionally, this plant was used as an antidote for poisoning. If one felt sleepy and suspected they were poisoned, they would take this plant to prevent the effects from taking hold.

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Australia:

Felted Anthotroche *(Anthotroche Pannosa)*

A lesser known plant, the felted anthotroche is a shrub commonly found in Western Australia and a more common source of ursolic acid. It was first discovered in 1839 by Stephan Edlicher, and is commonly found in more sandy environments such as dunes. They are described as having light petals with sometimes dark violet flowers attached in the center.

When dried, ursolic acid has been extracted from the felted anthotroche, giving the plant many of ursolic acid's signature biological properties, such as antibacterial properties,

protection against illnesses and anti-cancer properties. While not commonly explored in culture due to it's difficulty in accessibility, the plant itself still is a mainstay in research for triterpene extraction and analysis.

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What is Ursolic Acid?

Technical Definition

[1]Ursolic Acid is a terpenoid compound, meaning it is a part of a class of chemicals that are produced from isoprene. Terpenes are examples of organic and natural compounds that contain carbon and hydrogen. These chemicals are mainly created in plants and ursolic acid is a compound naturally found in fruit rinds. These types of compounds are the most abundant compounds found in plants and have various pharmacological functions as well (BYJUS). The wide range of shape and size in terpenoids allows them to have a large market. The chemical formula for ursolic acid is $C_{30}H_{48}O_3$ and it is classified as an organic compound.

Due to their large reach and various usages in our world Ursolic Acid and terpenoids are worth exploring. They can be used in various ways to solve problems that are currently facing our world.

Current Uses of Ursolic Acid

Ursolic Acid has diverse applications in health, nutrition, and research.

Health Supplements

[1] Apple Image: Image: *The Power of the Peel: 3 Benefits of Apple Skin You Never Hear About – SuperFoodsRx | Change Your Life with SuperFoods.* (2015, April 29). SuperFoodsRx |Change Your Life with SuperFoods. https://superfoodsrx.com/healthyliving/the-power-of-the-peel-3-benefits-of-apple-skin-you-never-hear-about/

Recently, there has been a boom in the supplemental world. With a boom in research and a shift to a more health conscious society, there has been an increased interest in exploring supplements and learning about their effect in the body. Ursolic Acid has already been approved as a dietary supplement by the FDA in America.

Ursolic Acid can be found in different types of dietary supplements because of its anti-inflammatory and antioxidant properties. It can help to combat oxidative stress and decrease chronic inflammation and can therefore be used to help individuals manage conditions such as cardiovascular disease or arthritis. It also has demonstrated benefits for muscle growth and fat loss and can be found in fitness supplements. Ursolic acid supplements can also be taken to help individuals regulate blood sugar levels and insulin sensitivity.

Ursolic Acid is also used by the fitness industry to enhance muscle recovery. Many athletes use the compound to help aid in building muscle after strenuous workouts. People also use the acid to reduce fat accumulation within their bodies. It is recommended to take about 450 mg of Ursolic Acid a day in order to see the effects of the drug (Patel).

Pharmaceutical Research

Ursolic Acid is of growing interest in the pharmaceutical research field. Recent studies are continuing to demonstrate the potential anticancer properties of ursolic acid, through inhibiting tumor growth, inducing tumor cell death, etc. These anticancer properties are studied in conjunction with current chemotherapeutic compounds to optimize the anticancer effect. Ursolic Acid is also being studied for its neuroprotective effects as a potential supplement for neurodegenerative diseases like Parkinson's or Alzheimer's. Furthermore, it also has a potential role in diabetes management with the ability to lower blood glucose levels.

Food Industry

Ursolic Acid has also been applied in the food industry because of its ability to serve as a nutritional additive and natural preservative. Due to its antioxidant properties, ursolic acid has the potential to extend the shelf life of food products by preventing spoilage. Specifically, it helps to prevent the oxidation of fats and oils in food products. It can also enhance the nutritional profiles of food products. Foods with ursolic acid can confer health benefits such as boosting metabolic health, reducing inflammation, and improving muscle function, which can make it appealing for health-conscious consumers.

750 × 500

There are many current applications for ursolic acid. It is clear that this is an important compound in our world that has an array of different uses. Actually, many scientists are continuing to investigate the role Ursolic Acid can play in medicine.

Current Scientific Interests

Ursolic Acid is currently being studied in relation to various diseases. Scientists are looking at its wide application and are discovering uses for the compound. As more funding and time gets poured into ursolic acid and searching for its effects within our bodies it seems as if there is a likelihood of more diseases getting reduced.

Liver Disease [2]

Only organs that are known to regenerate many people still have to receive liver transplants every year. The liver is a vital

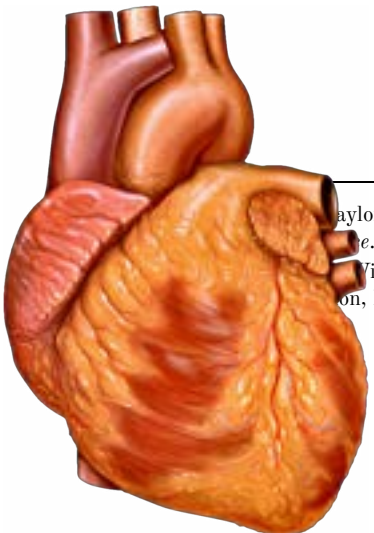
[2] Liver image: *Is your liver healthy? Know the 7 sign* Retrieved September 16, 2024, from https://www.healthcheckup.co.in/blog/is-

organ in our body that helps purify blood from different toxins that are in our body. There are many diseases that attack the liver causing people to need a liver transplant or to cut out portions of their liver. Some of these diseases include fatty liver disease and liver cancer. Scientists have recently been looking into your soul casted as a solution to many problems like these are liver. They found that overtime, using your Ursolic Acid decreased fatty liver disease biomarkers that indicate liver disease (Seo et. al). The studies were mostly done in mice but scientists are confident in their ability to one day see the same trends and people.

The Brain[3]

Ursolic acid has been shown to possibly be a method of preventative medicine against various brain diseases. This particular acid has been known to be a non-inflammatory treatment in various places of the body. This is especially helpful in the brain, as ursolic solid acid exhibits these same properties on this vital organ. Studies were done on rats where they treated them with ursolic acid and noticed a decreased expression of proteins that are known to cause cancerous tendencies in brain cells (Seo et. al). More than four separate studies were done on rodents relating to ursolic acid's effect on the brain and they all concluded that this compound has the potential to prevent various different kinds of brain disease.

The Heart[4]



Scientists have also started to explore ursolic acid and its benefits on the heart. Scientists have found that Ursolic Acid can lower the heart rate of patients which can aid in combating different

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types of heart diseases. Additionally, the acid has been explored for its use of increasing the amount of cardioprotective enzymes in heart tissues, and has the potential to protect the body against threats to the heart (Seo et. al). The ability to prevent and combat multiple types of cardiovascular disease draws scientists in to explore ursolic acid and the qualities it has to make it a useful drug to combat the greatest cause of mortality in our world: heart disease.

Diabetes[5]

In 2021, 11.9% of the United States or 38.4 million people had diabetes (CDC). Diabetes can be a difficult disease to manage especially with the prices of insulin rising. Some scientists have discovered that giving patients a dosage of Ursolic acid has decreased their overall blood sugar levels. These experiments were done both in the lab and in the body and both yielded significant results (Seo et. al). The acid is also currently being studied for its potential use in improving insulin sensitivity and glucose intolerance in people. Not only did Ursolic Acid help combat some symptoms of diabetes, it was also able to help patients decrease body weight and fat mass.

Conclusion

Ursolic Acid is a compound that seems to have no limits in the scientific world. It has been observed to have various properties that are useful in medication to combat a vast majority of diseases seen today. With more time and effort, scientists will continue to uncover the ways we can use ursolic acid to make our world a better place.

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