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RESEARCH GUIDE

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ARUM PALAESTINUM:
AN EMERGING NUTRACEUTICAL
FROM THE MEDITERRANEAN

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Each spring, in the rocky soils of Palestine, the Black Calla Lily blooms. Known also as Solomon's Lily or Priest's Hood, the local people of the Mediterranean region refer to this plant as "loof." Scientists call it *Arum Palaestinum*.

Growing like a weed in countries of the Mediterranean Basin, the leaves of *Arum palaestinum* are widely known and cherished as a traditional food and medicine. After boiling the leaves in water and cooking them with olive oil and lemon, people consume them as a delicacy—in part because of the belief that they might help to prevent colon cancer.

The roots of *Arum palaestinum* are tuberous, but its leaves are the part most highly valued for their nutritive properties.



In medical traditions among Jews and Arabs in Palestine, *Arum Palaestinum* has been employed to treat conditions that range from cancer to infections to intestinal worms. Extracts of the leaves maintain popularity today—as a part of Traditional Arabic Palestinian Herbal Medicine.

Arum palaestinum was little known in the United States until recent years. Its introduction to the US as an herbal supplement began when it was brought to the attention of a chemist by the name of Gene Zaid, PhD. Dr. Zaid is a Palestinian native who had migrated to the US in the 1960s. On a visit to the Middle East in 2005, an elder introduced him to the plant and its purported health benefits.

Dr. Zaid returned to the US and sought out to dissect the chemistry, synergistic compounds, and molecular mechanisms of this traditional plant. This was the beginning of the story of *Arum palaestinum* as an herbal supplement and inspiration for cancer-fighting pharmaceuticals in the US.

What is *Arum palaestinum*

Arum palaestinum is a flowering perennial of the Araceae family. Like other members of this family, its flowers have a characteristic central spike (called the spadix), surrounded by a curved petal (called the spathe). The flower is a deep purple or reddish-brown color, and its seeds are a vibrant red.

The roots of *Arum palaestinum* are tuberous, but its leaves are the part most highly valued for their nutritive properties. It should be noted that the leaves are high in oxalates, which can be neutralized by cooking. This may partly explain why traditional preparation methods have involved boiling the leaves in water or infusing them as a tea.

Arum palaestinum in the Mediterranean

Reports of *Arum palaestinum* as a food and medicine date back to the 9th century in Palestinian cultures. One of the most widely held popular beliefs has been that it helps to fend off cancer. The leaves were also believed to strengthen bones, treat kidney stones, and fight infections.

In modern-day Mediterranean regions, *Arum palaestinum* continues to enjoy popularity as both a food and herbal medicine. In a 2008 survey of 100 residents of

rural areas of Palestine, more than half of respondents reported the use of wild *Arum palaestinum* as a food. They most often prepared the leaves in the traditional way—boiled in water and then fried in oil and garnished with lemon.

In addition to eating the leaves as a food, people of the Middle East frequently take *Arum palaestinum* as an herbal medicine. In 2011, researchers surveyed 372 cancer patients in Palestine. Published in the *Journal of Ethnopharmacology*, the survey showed that *Arum palaestinum* was the most commonly used herbal product in the cohort.

Arum palaestinum in the United States

Arum palaestinum was never considered to be a food or medicine in the United States until it was brought to this country by Dr. Zaid. When he became inspired in 2005 to embark upon studying the plant, *Arum palaestinum* captured the attention of his friends and family—with eventual interest from clinicians and patients across the US.

Over the nearly 15 years since then, there have been published reports of the plant's chemical constituents, studies of how it works synergistically with other compounds, *in vitro* studies to explore the effects of the herb on both healthy and cancerous human cell lines, and *in vivo* studies to further assess its mechanisms and physiologic effects.

Because *Arum palaestinum* was not part of the US food supply before the passage of the Dietary Supplement Health and Education Act of 1994, safety studies were required before it could be sold as an herbal supplement. Those studies were completed, and *Arum palaestinum* became available in the United States in April 2018 as part of a formula called Afaya Plus.

Chemical Constituents

The first comprehensive profile of the chemical constituents of *Arum palaestinum* was published in 2015—identifying its leaves as a rich source of antioxidants and phenolic compounds.

Published in *Food Research International*, the profile of a hydro-methanolic extraction of the leaves reported a total of 180 phytochemicals. Among the compounds detected in the plant were 53 flavonoids, 33 phenolic acids, 10 terpenoids, 7 iridoids, and 6 amino acids.

Fortification with Active Compounds

One challenge with utilizing herbs as nutraceutical supplements is the inherent lack of standardization. The concentration of active compounds varies from batch to batch, depending on the season and growing conditions for the herb. One way to ensure a standardized product is to fortify herbal extracts with known amounts of active constituents.

After isovanillin, linolenic acid, and beta-sitosterol were determined to be major constituents in the aqueous extract of *Arum palaestinum*, researchers set out to develop an herbal extract fortified with these compounds. The result was a formulation called GZ17. GZ17 has since been evaluated in preclinical studies.

- **Isovanillin.** Isovanillin is a phenolic aldehyde that is naturally occurring in some plants and is used to flavor food. Scientific studies on this compound are minimal, but there is some preclinical evidence that it may support gastrointestinal and cellular health.
- **Linolenic acid.** Linolenic acid is an omega-3 fatty acid that is present in many plant foods, nuts, and seeds. Studies suggest that it supports cardiovascular health and a healthy inflammatory response.
- **Beta-sitosterol.** Beta-sitosterol is a plant sterol found in many fruits, vegetables, nuts, and seeds. It is best known for its role in supporting prostate health. It is also used to support healthy cholesterol levels and lipid metabolism. There is some preclinical evidence that beta-sitosterol works as an immunomodulating agent.

Although the GZ17 formulation of *Arum palaestinum* has only been used in research studies, similar combinations are available as over-the-counter medications or dietary supplements.

In addition to the 2015 report, earlier studies had isolated 2 flavone C-glucosides (isoorientin and vitexin) and identified caffeic acid, luteolin, and vicenin 11 in the leaves of *Arum palaestinum*.

From evaluations of the aqueous extract of *Arum palaestinum*, 3 major compounds stood out: isovanillin (a phenolic aldehyde), beta-sitosterol (a phytosterol), and linolenic acid (a fatty acid). Those compounds have since been used to fortify extracts of *Arum palaestinum*. Both the fortified combination and individual compounds have been subjected to preclinical studies.

Mechanisms of Action

The studies of the chemical constituents of *Arum palaestinum* showed that it is rich in phenolic compounds, and subsequent studies have shown that the phenolic content directly correlates with its antioxidant capacity. A strong ability to scavenge free radicals is one of the best-established mechanisms of this plant's action.

Mechanistic studies have also revealed that various preparations of *Arum palaestinum* target multiple metabolic pathways. Two separate studies have determined that extracts of the herb induce apoptosis by activating

Synergistic Combinations

In the tradition of herbal medicine, rarely are herbs taken alone. Herbs are often combined with other herbs or with active constituents for synergistic effects. Some of the herbs and active constituents that have been evaluated in combination with *Arum palaestinum* include *Peganum harmala* and *Curcuma longa*.

- ***Peganum harmala*.** *Peganum harmala*, also called Syrian rue, is also native to the Mediterranean region and to herbal traditions in the Middle East. All parts of the plant can be used, but most commonly the seeds are used. People have historically ingested the seeds by decocting them for a tea or preparing them for smoking. Topical preparations are also common.
- ***Peganum harmala*** is used by cancer patients and for anti-inflammatory purposes throughout the Middle East. One of the active constituents of *Peganum harmala* is harmine. Harmine can be toxic and psychoactive in large doses but is therapeutic in small amounts. Harmine is a monoamine oxidase (MAO) inhibitor, might reverse resistance to anti-cancer drugs, and is active against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).
- ***Curcuma longa*.** *Curcuma longa*, commonly known as turmeric, is widely used around the world as a food and medicine. The active constituent in *Curcuma longa* is curcumin, which has demonstrated anti-inflammatory and antioxidant activity. Curcumin has also been shown to potentiate the efficacy of other nutraceuticals as well as chemotherapeutic medications. Curcumin can be combined with *Arum palaestinum* to support antioxidant defenses and cellular health.

caspase proteins (caspase-3 and caspase-6). Some preparations have also been found to inhibit molecular signaling cascades that include epidermal growth factor receptor (EGFR), extracellular signal-regulated protein kinases 1 and 2 (ERK 1/2), and protein kinase B (AKT).

Safety

Preliminary safety studies of *Arum palaestinum* were conducted by administering a preparation of the herb to rats in an amount of 5,000 mg/kg for 14 days. A GZ17 formulation of *Arum palaestinum* was then administered in an extremely high daily dose of 1,000 mg/kg for 21 days—as part of a study of tumor growth in rats. This amount still led to no apparent adverse effects or changes in any organs.

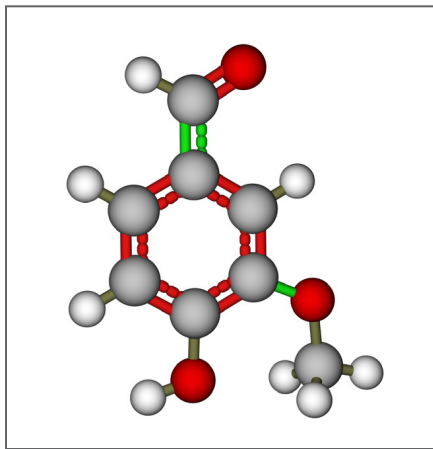
Despite no formal safety studies in humans, substantial evidence for the safety of *Arum palaestinum* comes from its long tradition of use. Recently in 16 Middle Eastern countries, researchers surveyed 339 oncology healthcare providers about their experience with herbal supplements. Of the 44 herbs that practitioners reported using, there were safety concerns for 29. The authors of the study, which was published in *Cancer* in 2016, found no drug-herb interactions or safety issues associated with *Arum Palaestinum* in cancer patients.

Preparations

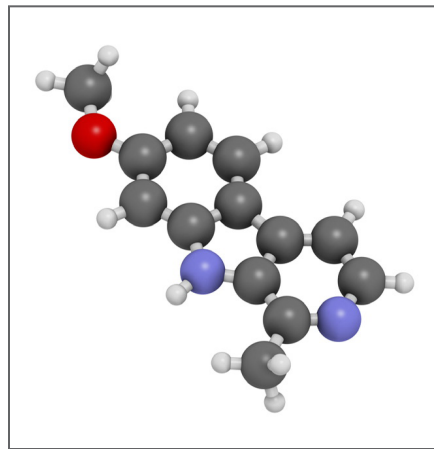
Tea is the most frequently used preparation of *Arum palaestinum* as a traditional herbal medicine. According to a survey of herbalists and traditional healers in Palestine that was published in 2016, the most reported way to prepare the herb was to boil 10 grams of leaves in 150 mL of water. This tea was recommended to be consumed 3 times a day before meals.

Because tea was the traditional preparation of the herb, this is the form that Dr. Zaid shared with his friends and family members after returning from Palestine with knowledge of the herb. Many people he knew began to drink the tea because of the supposed health benefits. The problem was that it tasted horrible. Although the numbing effect of the fresh leaves can be reduced by cooking or drying, the tea is reportedly still offensive to drink.

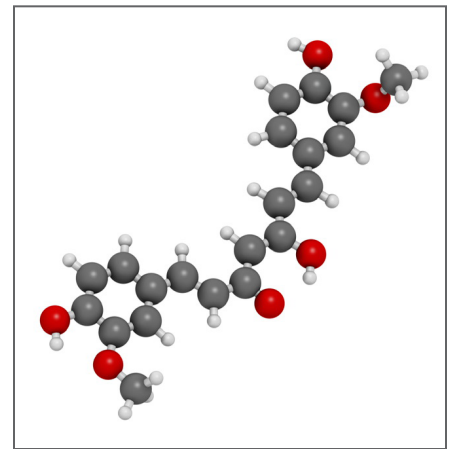
To overcome the issue of taste, Dr. Zaid set out to develop a preparation of *Arum palaestinum* that could be delivered in capsules. After comparing the



vanillin



harmine



curcumin

phenolic content and antioxidant activity of fresh, roasted, shade-dried, and boiled leaves of the plant, he and his team concluded that roasting was the most effective method of preparing *Arum palaestinum* for nutritional supplements.

Preliminary Research

One of the earliest studies to explore the *in vitro* effects of *Arum palaestinum* was published in 2007 in the *Archives of Pharmacal Research*. This study found that an ethanol acetate-extract of *Arum palaestinum* had a strong ability to scavenge free radicals and to suppress the proliferation of human breast cancer cells and lymphoblastic leukemia cells. However, the same study found that the extract failed to suppress the growth of a line of liver cancer cells.

Then in 2015, a study published in the *Asian Pacific Journal of Tropical Biomedicine* showed for the first time that a diethyl ether-extract of *Arum palaestinum* had *in vitro* antiproliferative activity against 4 human cancer cell lines (larynx, cervix, liver, and breast). The study also reported that 4 isolated flavonoid compounds from *Arum palaestinum* (luteolin, chrysoeriol, isoorientin, and isovitexin) showed moderate antitumor activity.

Another 2015 study, published in *BMC Complementary and Alternative Medicine*, evaluated the anti-cancer activity of a fortified version of *Arum palaestinum* against androgen-independent prostate cancer models *in vitro* and *in vivo*. An aqueous extract of *Arum palaestinum* roots and leaves was fortified with known quantities of isovanillin, linolenic acid, and beta-sitosterol (GZ17). This combination was tested for its effect on prostate

Results from the 2018 study showed that the most effective formulation was the one with only 3 isolated synthetic components—isoavanillin, harmine, and curcumin. This formulation decreased cancer cell proliferation of not only HNSCC cells but also glioblastoma and lung cancer cell lines.

cancer cells and healthy human cells *in vitro* and for its effect on mice with tumors derived from prostate cancer cell lines.

The studies showed that the fortified extract of *Arum palaestinum* suppressed the growth of human prostate cancer cell lines without causing any cell death to healthy human cells. The extract also suppressed the growth of prostate tumors in mice. What's more interesting is that each of the individual fortifying components (isoavanillin, linolenic acid, and beta-sitosterol) was ineffective at suppressing the growth of prostate cancer cell lines when administered alone—evidence of the importance of synergy.

The most recent study of *Arum palaestinum* and its isolated compounds was published in 2018 in *Scientific Reports*. The study evaluated the antitumor effects of 3 different formulations against head and neck squamous cell carcinoma (HNSCC) *in vitro* and *in vivo*. The

first formulation was a combination of plant extracts (*Arum palaestinum*, *Peganum harmala*, and *Curcuma longa*). The second was a combination of 16 synthetic components from these plants. The third was a combination of 3 synthetic components (isovanillin, harmine, and curcumin).

Results from the 2018 study showed that the most effective formulation was the one with only 3 isolated synthetic components—*isovanillin*, *harmine*, and *curcumin*. This formulation decreased cancer cell proliferation of not only HNSCC cells but also glioblastoma and lung cancer cell lines. It also decreased angiogenesis, mitigated invasion of HNSCC cells, and enhanced the effects of standard chemotherapy *in vitro*.

Clinical Potential and Future Research

Arum palaestinum has a long history of traditional use and promising preclinical research, but there is a noticeable absence of human clinical trial data for this herbal extract. That will hopefully change in the coming years. Now that there is preliminary evidence for its safety and mechanisms, researchers have grounds to initiate clinical studies.

One emerging area of interest for the clinical potential of *Arum palaestinum* is for helping to soften cold sores and fever blisters caused by the herpes simplex virus. When combined with *Peganum harmala* and *Curcuma longa*, the combination may help support antiviral and antioxidant defenses.

Another area of interest for future research spawns from the preclinical trials—for the support of cellular health. The *in vitro* and *in vivo* studies described in this research guide show that *Arum palaestinum* might possess properties to support numerous cellular pathways for health.

It's exciting to note that the early successes seen with *Arum palaestinum* and its synergistic formulations have inspired world-class, pharmaceutical-grade research. The combination of 3 synthetic compounds (*isovanillin*, *curcumin*, and *harmine*) from 3 synergistic herbs goes by the drug name of GZ17-6.02 and is manufactured by Genzada Pharmaceuticals. This drug has shown promise in preclinical studies of pancreatic ductal adenocarcinoma and is currently in phase I clinical trials with patients with advanced solid tumors or lymphoma.

Where to Find *Arum palaestinum*

Arum palaestinum comes from a long history of use by natives of the Mediterranean region. Since learning about this herb in 2005, chemist Dr. Gene Zaid has been committed to supporting research on the plant's chemistry, mechanisms, and clinical potential.

The discovery of the major chemical constituents of the plant has led to formulations that are fortified with these active compounds or combined with additional herbs for synergy. Encouraging results of preclinical trials have also spawned the development of a drug that is undergoing phase I clinical trials.

Arum palaestinum is currently available as a supplement in combination with synergistic herbs (*turmeric*, *harmala*, and *garlic*) and compounds (*vanillin* and *beta-sitosterol*). This formulation is manufactured by Hyatt Life Sciences and is called Afaya Plus. A topical formulation that includes similar ingredients is currently available as an over-the-counter preparation by the name of Arumacil.

About the Author

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