

Exploring *Ferula assa-foetida*'s Potential in Combating *Helicobacter pylori* and Gastric Cancer

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ABSTRACT

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Helicobacter pylori is one of the most effective factors in digestive diseases. Infections caused by this bacterium are prevalent and affect many people worldwide yearly. The stages of the spread of this infection are as follows: first, the bacteria are concentrated in the area of the cardia stomach valve and leads to irritation in this area. Then the proliferation of bacteria spreads and penetrates the lining tissues of the stomach, which leads to severe inflammation in the stomach. In the advanced stages of infection, it becomes cancerous and metastasized, so that even with surgery and removal of a part of the stomach, bacteria and secondary tumors grow, spread, and transfer aggressively. In general, this infection is directly related to economic, social, and health conditions. Today, many drugs are used by patients to treat these bacteria. But the point that should be paid attention to is the prevention of this infection. Observing health issues and benefiting from digestive medicinal plants can play a significant role in the recovery of patients. Therefore, we decided to investigate the potential and evaluation of the medicinal plant *Ferula assa-foetida* L., which is one of the suitable candidates for the prevention and treatment of this infection. The results of this research showed a promising perspective so it was found that the use of *F. assa-foetida* and its effective ingredients have a significant effect in controlling infection in patients. It was also found that the use of *F. assa-foetida* extract leads to an increase in apoptosis and necrosis in gastric cancer cells, especially in high concentrations of 1500 µg/ml. On the other hand, this study provided a wide field of pharmaceutical research related to drug production and treatment of gastrointestinal diseases. It is hoped that by focusing on this research and using the medicinal properties of these valuable plants, it will be possible to completely prevent the proliferation of these bacteria in the stomach and provide the basis for the treatment of patients.

Keywords: Cardiovascular diseases, Ferutinin, Galbanic Acid, Peptic Ulcers, Umbelliprenin

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INTRODUCTION

F. assa-foetida is one of the most important and oldest medicinal plants native to the steppe regions of Iran and Afghanistan. This plant has many phytochemical properties and biological and physiological activities [1-3]. Currently, this plant is widely cultivated in Iran, Afghanistan, and India. *F. assa-foetida* grows in Iran in the southern parts and central mountains of Zagros, as well as in areas with weak vegetation next to thorny and short plants. For this reason, when it flowers and reaches a height of two meters, it is completely distinguishable from other plants. *F. assa-foetida* belongs to the *Apiaceae* family, it is a perennial and herbaceous plant that has a rather pungent smell similar to the smell of garlic [4-6]. Its flowers are yellow, its leaves are fleshy, and it has thick and straight roots. *F. assa-foetida* flowers only once during its growing season. Generally, this plant is a multifaceted plant in that

it has both medicinal properties and agricultural and industrial uses. This plant contains many secondary metabolites and antioxidants that are very effective in the treatment of digestive and cardiovascular diseases [7].

This medicinal plant has been used since ancient times in the treatment of many diseases, especially digestive diseases. Generally, *F. assa-foetida* contains many chemical compounds. These compounds play an effective role in the treatment and prevention of a wide range of diseases with their antioxidant properties and eliminating many free radicals. Compounds such as disulfides, polyphenols, and monoterpenes in *F. assa-foetida* play an important role in neutralizing free radicals. Also, this plant contains many biologically active compounds such as auraptene, umbelliprenin, galbanic acid, daucane esters, ferutinin, ferulenol, and ferprenin. These biologically active compounds, which have

antioxidant properties, prevent many diseases such as liver, gastric, and intestinal cancer. But one of the most important compounds in *F. assa-foetida* is the resin gum of this plant. *F. assa-foetida* contains 20% essential oil, 60% resin, and 25% gum [8-10].

Gum and resin are among the most important components of this plant. The most important property of the resin is the analgesic effect of this compound. So that this substance is used to reduce menstrual pains, relieve toothache, and relieve stomach pain and spasms [8-10].

F. assa-foetida is one of the most important medicinal plants related to digestive diseases. In addition, this plant has very effective effects in the treatment of other diseases such as constipation, diarrhea, jaundice, and diseases related to ear, nose, throat, and vision. Although this plant is specific to hot and dry regions, it has many healing properties for skin and hair-related diseases and plays an important role in its health and shines through moisturizing properties and increasing oxygen supply to the skin and hair. *F. assa-foetida* also responds positively to skin allergies and insect bites and disinfects the skin against insect bites [11-13].

F. assa-foetida also has many anti-pain and anti-inflammatory properties, so it prevents any infection after childbirth and reduces menstrual pains. This plant contains many compounds of coumarin, so through these compounds, it causes blood thinning and blood pressure reduction. This plant is also recommended for oral and dental health and has very beneficial effects in preventing tooth decay. Also, this medicinal plant contains chemical compounds and antioxidants such as various polyphenols that are used in the treatment of various cancers [11-13]. But the most important property of this plant is related to digestive diseases of the stomach and intestines. So its consumption plays an important role in reducing gastric and intestinal cancer. Relief of stomach pains, treatment of digestive disorders such as diarrhea, digestive ulcers such as stomach ulcers, flatulence, food poisoning, and serious diseases of the digestive system such as gastric and colon cancer are among the important therapeutic properties of *F. assa-foetida* [14-16].

Gastric cancer is a big problem and an unpleasant challenge for the world during the past years. Every year, many people in the world are infected with this disease and suffer from it. Gastric cancer is the fifth most common cancer in the world and unfortunately, it is the third most common cause of death from cancer. According to research conducted in 2020, it was found that more than one

million people around the world are suffering from this disease [17-19]. Generally, the incidence of this disease is different in men and women, and men are affected by this disease 2.4 times more than women. Generally, it can be said that many factors are involved in the occurrence of gastric cancer. Chemical factors, smoking, alcohol, processed foods, and exposure to dangerous rays increase the risk of contracting this disease [17, 18, 20].

According to the studies, it has been found that regions like East Asia and Central Europe have recorded the highest rate of this disease. Although this disease is also very widespread among black people and low social and economic classes. The increase in peak incidence can be caused by excessive consumption of alcoholic beverages, improper nutrition such as excessive consumption of salt and lack of vegetables in the diet, and smoking. Generally, the main way to treat this disease is surgery, and in the acute stages, which usually last less than a year, pain relief and management to reduce the symptoms of the disease are on the agenda. However, if diagnosed in the early stages of this disease, it can be treated through chemotherapy. Today, countries such as Japan and the United States have seriously screened for this disease, which has significantly reduced the death rate caused by this disease [17, 18, 20, 21].

During the past years, human cancers have caused very high mortality [22]. So that according to the estimated statistics in 2020, more than 19 million new cases of this disease have been identified, and about 10 million of them died. Generally, it can be said that about 10% of these cases have a genetic and hereditary background, but if we have a general division about human cancers, we will find that almost half of the cancers have microbial and viral origins. Pharmacological and epidemiological studies show that bacteria are also closely related to human cancers [23-25].

The International Agency for Research on Cancer (IARC) announced in one of the most important classifications related to types of human cancers that *H. pylori* is the only class I human pathogen in humans that causes infection and gastric cancer (Fig. 1) [23-25]. Also, the research results of this center showed that this bacterial carcinogenic factor increases cell proliferation, inflammation, interstitial damage, and signaling changes in cells [26, 27]. Considering that every year, many people in the world are affected by this bacterium, we decided to investigate the effect of *F. assa-foetida* medicinal plant extract treatment and its different concentrations on *H. pylori* bacteria and gastric cancer cells [23-25].



Fig. 1 Electron microscope images of *H. pylori* bacteria

In this research, we investigated two major tumor suppressor genes, *ZNF292* and *RUNX3*. The *ZNF292* gene is a highly active

transcription factor dependent on the growth hormone. The N-terminal region of this gene contains 4 zinc fingers. However, the

C-terminal region has more DNA binding sites. This gene is one of the important tumor suppressor genes in stomach cancer. Regarding the *RUNX3* gene, it should be said that this gene plays a role in controlling gastric endothelial cells by activating alpha and beta factors as well as affecting *CBFB* genes. Also, recent research has shown that this gene is involved in epigenetic processes and activation of lymphocytes, and in general, the *RUNX3* gene is one of the important factors in tumor suppression, especially tumors related to stomach cancer. Figure 2 shows the exact location of these genes in the cell. As seen in Figure 2, the *ZNF292* gene is mostly produced in the cell nucleus, and the *RUNX3* gene is produced both in the nucleus and in the cytoplasm.

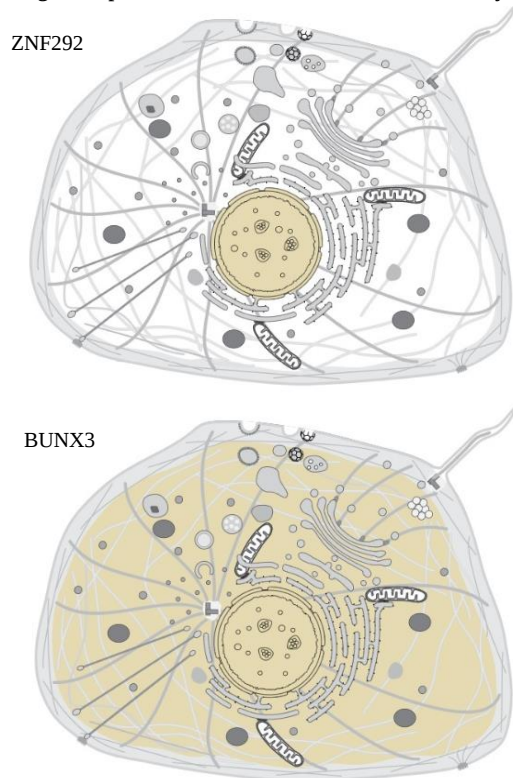


Fig. 2 On the left side, it shows the location of *ZNF292* gene production in the cell. On the right side, it shows the location of *RUNX3* gene production in the cell.

MATERIALS AND METHODS

First, the *F. assa-foetida* plant extract was prepared by the Giyahkala Company. Then 10 mg/ml of the solution was cultured in a PBS medium. Then it was sterilized by a 0.2-micron filter and kept in the refrigerator until use. To investigate the effects of *H. pylori* and gastric cancer, gastric adenocarcinoma cells were used. Thus, this cell line was first cultured in a DMEM medium containing penicillin, streptomycin, and FCS-enriched serum. Then, to check different tests, the cells were separated by trypsin and EDTA solution and after washing, the percentage of cell survival was determined using Trypan blue by Hemocytometer. In this research, cells with a viability percentage higher than 90% were used. Finally, to check the rate of cell growth and proliferation, the MTT colorimetric method was used with the number of 2×10^4 gastric adenocarcinoma cells. These cells were examined in microplate wells in three replicates. Then, the treatment of *F. assa-foetida* extract with concentrations of 500 $\mu\text{g/ml}$, 1000 $\mu\text{g/ml}$, 1500 $\mu\text{g/ml}$, 2000 $\mu\text{g/ml}$, and 2500 $\mu\text{g/ml}$ was applied to them and they were incubated for 24 hours. Then 5 $\mu\text{g/ml}$ of MTT solution was added to each well and incubation was done again for 3 hours. After that, the amount of 2 $\mu\text{g/ml}$ of DMSO

solution was added to each well and the optical absorbance was read at a wavelength of 545 nm.

Examining the Amount of Apoptosis and Necrosis in Cells

In this case, the number of 5×10^5 cancer cells was examined in three replicates in 15 sinks. First, the cells were treated with concentrations of 500 $\mu\text{g/ml}$, 1000 $\mu\text{g/ml}$, 1500 $\mu\text{g/ml}$, 2000 $\mu\text{g/ml}$, and 2500 $\mu\text{g/ml}$ of *F. assa-foetida* extract. Then incubation was done for 24 hours and in the next step the cells were analyzed by flow cytometry. In this research, the amount of Annexin V-FITC/PI cell population was considered as an indicator of apoptosis and necrosis. Finally, the statistical analysis was analyzed by SPSS software at the level of 5%.

RESULTS AND DISCUSSION

Generally, the purpose of this research was to investigate cell proliferation, apoptosis, and necrosis in gastric cancer cells that were affected by *H. pylori* bacteria. Therefore, this investigation was done in three replicates and 15 sinks independently to investigate cell proliferation, apoptosis effects, and necrosis. The results of this research showed that the extract of *F. assa-foetida* reduces the growth and proliferation of cancer cells, and as seen in Figure 1, increasing the concentration of the extract of *F. assa-foetida* has shown a great effect in reducing the growth of cancer cells (Fig. 3).

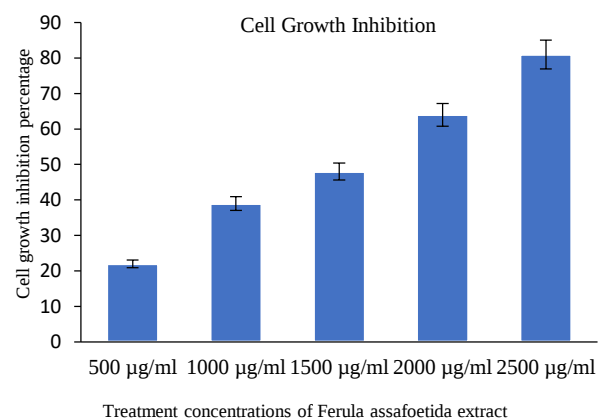


Fig. 3 Proliferation of gastric cancer cells under the influence of *F. assa-foetida* extract treatment.

The results of the investigation of apoptosis in gastric cancer cells also showed that *F. assa-foetida* extract in concentrations of 1500 $\mu\text{g/ml}$, 2000 $\mu\text{g/ml}$, and 2500 $\mu\text{g/ml}$ significantly increases apoptosis. However as seen in Figure 4, the extract of this plant in low concentrations does not have much effect on apoptosis. Therefore, the use of this Figure can determine the optimal concentration for the use of *F. assa-foetida* extract in cancer cells. Meanwhile, the graph of necrotic effects under the influence of *F. assa-foetida* extract showed that increasing the concentration in a stepped manner has a positive effect on the necrosis of cancer cells (Fig. 5).

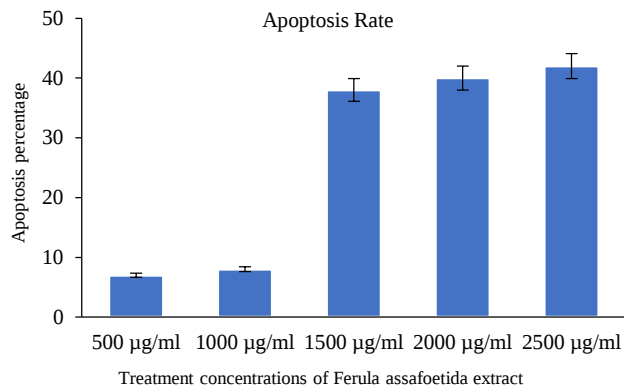


Fig. 4 Apoptosis in gastric cancer cells under the influence of *F. assa-foetida* extract treatment

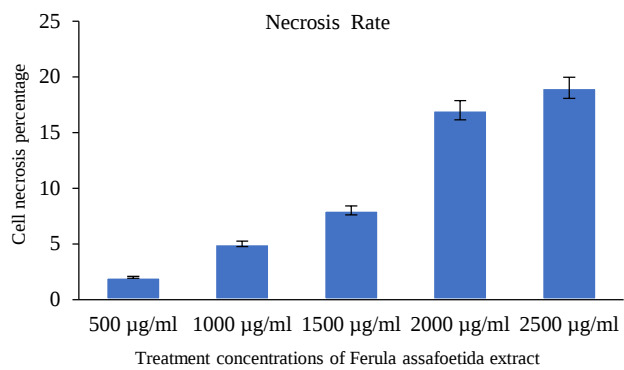


Fig. 5 Necrosis in gastric cancer cells under the influence of *F. assa-foetida* extract treatment.

Table 1 Genes sequence results of *ZNF292*, and *RUNX3*

Name	ZNF292	RUNX3
ORGANISM	Homo sapiens (Human)	Homo sapiens (Human)
Accession number nucleotide	NM_015021.3	NM_004350.3
Accession number protein	NP_055836.1	NP_004341.1
Gene ID	23036	864
Chromosome	6	1
Molecular function	DNA-binding	DNA-binding/Activator
Cytogenetic location	6q14.3	1p36.11
Chromosome location bp	87155565-87265943	24899511-24965138
nucleotide length	12341 bp	4267 bp
protein length	2723 aa	415 aa
Molecular weight (Da)	304815.68	44355.54
Isoelectric point	7.27	9.53
Total Exon	8	5

Generally, herbal treatments are among the common methods for treating diseases such as fever, inflammation, and pain, and generally, there is not enough information about their mechanism of action. Today, stomach cancer caused by *H. pylori* bacteria is the biggest cause of stomach cancer deaths in the world. For this reason, research and production of anticancer drugs with more efficiency and less toxicity are necessary to control it. The effectiveness of many obtained compounds that are the result of plant extracts in the prevention or treatment of cancer has been confirmed in the laboratory. In the meantime, the medicinal plant *F. assa-foetida* and its extract, which is widely used in traditional medicine, has always been considered a promising factor, antibacterial and repellent to carcinogenic toxins. Recent research shows that *F. assa-foetida* extract can destroy cancer cells through antioxidant and molecular mechanisms. As we have seen in this research, it was found that *F. assa-foetida* extract greatly reduces the proliferation of cancer cells [28-30].

Bioinformatic Analysis of Genes

Research conducted in recent years has clearly shown the connection between genetic mechanisms and cancer tumors. In this regard, in this study, we investigated the bioinformatics of two unique types of gastric cancer tumor suppressor genes, *ZNF292* and *RUNX3*. The results of bioinformatics analysis, including Gene ID, the exact location of the gene on the chromosome, molecular weight, isoelectric point, and other features of the genes are briefly shown in Table 1. On the other hand, considering that the exact understanding of the mechanism of the effect of these factors requires a protein study, first the three-dimensional structure of these proteins was drawn through the swissmodel database. Considering that the value of GMQE shows an accurate estimate of the three-dimensional structure, we used this index to examine the three-dimensional structure of proteins. The results of this investigation in the protein related to *ZNF292* and *RUNX3* genes were equal to 0.48 and 0.31, respectively. As a result, it was found that these structures are accurate estimates of the desired proteins. Figure 6 clearly shows the three-dimensional structure of these proteins. So this review reveals the differences between these proteins.

Then, to check the stability of these proteins, Ramachandran's diagram was used according to the angles ϕ and ψ . Considering that the amount of Ramachandran Favored in the structure of *ZNF292* and *RUNX3* was equal to 87.22% and 68.04%, respectively, it was found that these proteins are in a stable state and the structure of *ZNF292* is relatively more stable (Fig. 7).

It has been shown that *F. assa-foetida* extracts through monoterpenes, sulfide compounds, and polyphenols can be very promising in the treatment of gastric cancer. Contrarily, the role of this plant in controlling and improving other types of cancer has also been reported[15]. It has been clearly shown that the amount of apoptosis and then necrosis of cancer cells increases under the influence of *F. assa-foetida* extract [16, 18]. The results obtained from examining the treatment of *F. assa-foetida* on stomach cancer cells by previus research that it confirms this case [14].

It has been investigated various types of cancerous lesions, especially gastric cancer, and concluded that there is always a balance between apoptosis and cell proliferation, and this balance can be disturbed in the presence of *H. pylori* , gene mutations, and changes in regulatory factors [31].

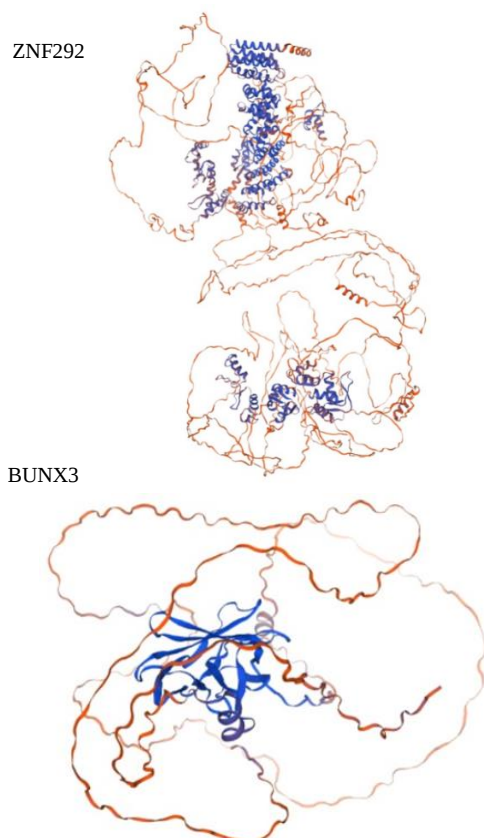


Fig. 6 On the left side, is the three-dimensional structure of ZNF292 protein. On the right side, is the three-dimensional structure of RUNX3 protein.

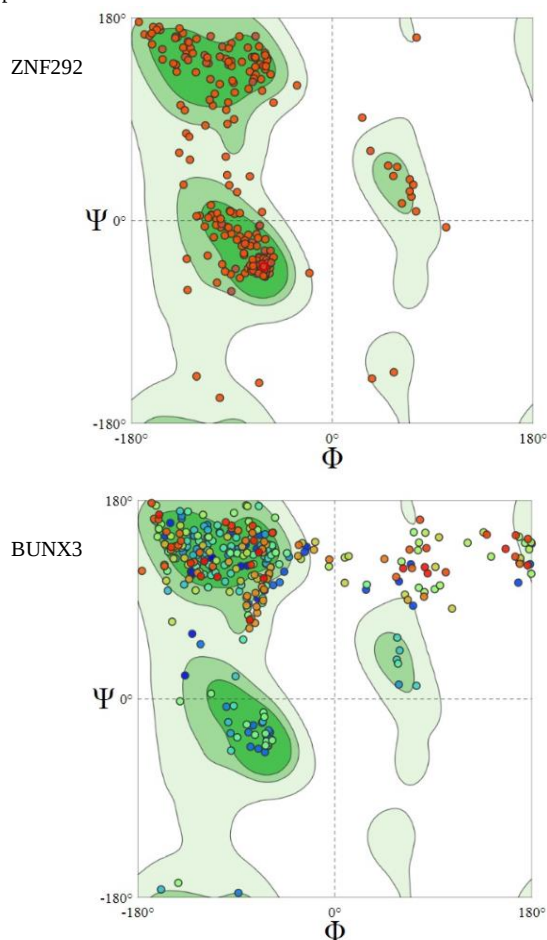


Fig. 7 On the left is the Ramachandran diagram of ZNF292. On the right is the Ramachandran RUNX3 chart.

Contrarily, many studies have shown that *H. pylori* infection can inhibit the apoptosis of neutrophils and create a positive effect in controlling gastric cancer. Contrarily, *H. pylori* infection leads to the activation of compounds such as interleukin through the autophagy mechanism. Generally, it can be concluded that exposure to *H. pylori* and its secreted factors can be used as a suitable strategy for the treatment of stomach cancer [32]. Regarding the use of *F. assa-foetida*, according to recent research, it can be said that the increase in cell apoptosis and necrosis under the influence of *F. assa-foetida* extract can be due to the stimulation of pro-inflammatory proteins. The stimulation of these proteins can also increase mucosal inflammation caused by *H. pylori* in the stomach and ultimately contribute to the pathogenesis of gastric cancer [33].

It has been investigated the anti-tumor effects of apoptosis in breast cancer cells in mice. These studies also showed that *F. assa-foetida* has a positive and great effect in increasing apoptosis and causing the destruction of cancerous tumors. Most of these studies point to the role of antioxidants and secondary metabolites in *F. assa-foetida*. This case shows that with a detailed and comprehensive investigation, the molecular role of *F. assa-foetida* in reducing anti-tumor effects can be understood. Although there are many factors involved in this process, the limitations caused by them should be reduced. It is hoped that the collection of this research will reveal the general molecular path leading to these processes so that by inducing more of these antioxidants, they will help to cure cancer patients and eradicate these bacteria [14].

CONCLUSION

The human body deals with external factors through the secretion of stomach acid in the mucous layers, and this factor acts as the first defense system of the body. Heartburn is the first sign of bacterial infection. The stomach tries to fight the growth of bacteria by secreting more acid. These effects cause damage to the areas of the esophagus, fundus, and cardia. Due to the absence of epithelial tissue in the esophagus, the effects of stomach acid cause pain and burning. For this reason, patients also use drugs that reduce stomach acid in the treatment process. As a result, if you feel a burning sensation in the area of the esophagus, fundus, or cardia, necessary action should be taken quickly to deal with the bacteria. The use of effective medicinal plants such as *F. assa-foetida*, which contains many antioxidant compounds, especially in dealing with digestive diseases, can prevent the harmful effects of these bacteria in the early stages. While including this plant in the food plan, it will have very beneficial effects in preventing digestive diseases.

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