

## Medicinal Plants, Effective Plant Compounds (Compositions) and their Effects on Stomach Cancer

### Abstract

Medicinal plants have special importance around the world. Further, they have been noticed for nutrition and illness treatment such as preparation of anticancer new drugs. Therefore, a wide range of studies have been done on different plants, and their anticancer effects have been investigated. Nowadays, cancer is the most important factor of death rate in the developed and developing countries. Among them, stomach cancer is one of the most common malignancies around the world. At present, it is recognized as the fourth common cancer and the second factor of death rate due to cancer. So far, there has been wide range of effort for cancer treatment; however, in most cases, the response to the treatment has been very weak and often accompanied improper subsidiary effects. The present problems as a consequence of chemical treatment and radiotherapy and many subsidiary problems created due to their use for patients, and also, the resistance to the current treatment has motivated researchers to apply new medicines with more effect and less toxicity. The secondary metabolisms existent in the plants have an important role in the treatment of several diseases such as cancer. This study was conducted to investigate and collect scientific results for stomach cancer and to clarify the role of medicinal plants and secondary plant compounds on its treatment.

**Keywords:** Medicinal, plants, stomach cancer, therapeutics

### Introduction

Nowadays, cancer is one of the most important problems dealing with medical science; the number of victims and those people who afflicted to this disease is increasing greatly. Among these, stomach cancer is the most important and fourth common cancer around the world. It is the second factor of death rate due to cancer. At present, several methods are used for cancer treatment; however, unfortunately, in most cases, the response to the treatment is very weak and causes improper subsidiary effects. Nowadays, because of the increase of death rate due to cancer and deficiency of chemical therapy and radiotherapy in advance forms, a need to find new methods to control cancer is essential.<sup>[1-6]</sup> At present century, there is wide range of researches on medicinal plants, and the introduction of medicines with natural effective compounds opens new horizons toward physicians and chemists association.<sup>[7-11]</sup> So that at present time, one-third of the applicable medications in human community have been made from natural and herbal resources, and physicians believe that patients should be encouraged

to consume herbal plants. In this regard, in recent decades, chemists have made various medicines based on the herbal extracts and presented to the market that their positive effects have been confirmed by physicians, researchers, and people.<sup>[12-17]</sup> These plants have been used for various diseases including cancer.<sup>[18-29]</sup> There have been some efforts for cancer treatment; however, unfortunately, in most cases, the response to treatment has been weak and often included the improper subsidiary effects.<sup>[30,31]</sup> The present problems in the application of chemical therapy and radiotherapy and several subsidiary problems created for patients, and also, the cancerous cells resistant to the common treatments lead to the application of new medicines with more effects and less toxicity.<sup>[30-34]</sup> The secondary metabolites are examples of these compounds that have very important role in several illness treatments such as cancer. With regard to the fact that the secondary plant metabolites have great therapy potential, hence, we investigated the important medicinal plants and their effective compounds for stomach cancer treatment. On the other hand, since the

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clinical symptoms and the prevalence of stomach cancer are different in various communities, more knowledge about involvement, clinical symptoms, and stomach cancer prevalence might have important roles in stomach cancer prevalence which might have an important role in time recognition and treatment of cancer. This research was aimed at investigation and gathering of scientific texts about stomach cancer and the role of medicinal plants and secondary plant compounds on its treatment.

### The Cancer Mechanism and Tumor Creation

Lack of tumor control genes causes the uncontrollable division of cancer cells. One of the inhibitor genes is P53 which on chromosome 17 P13.1. When this gene mutates, it causes an unusual protein synthesis. At this time, opposite to its natural operation destroys all the genes that work under the effect of this protein. Some molecules and biologic cell division processes also change the path.<sup>[35-37]</sup> The gene mutation and mutated sequences distribution in different cancers are different.<sup>[38]</sup> As it was said, cancer is considered as a consequence of cell's exit from the correct path of adjusted, proliferative, and distinctive approach. Lack of sensibility to inhibit signals, avoidance from programmed cell death, indefinite potential of proliferation, keeping angiogenic, tissue invasion, and metastasis all may lead to malignancy and cancer. A tumor cell that has more repetitive division than other cells has changed surface features. Furthermore, it loses the specificity of the cell that derived from it. A malignant tumor influences near the tissues and can link to the basic membrane and enzymes secretion that influences and leads to bloodstream which help metastasis. Each drug usually has a specific site to act.<sup>[39-46]</sup> This is the same for anticancer drugs. Medicinal plants also use these sites for their actions.

### Factors Related to the Increase of Stomach Cancer

Generally, the clinical symptoms of stomach cancer in primary phases are not specific, and because of ambiguity and lack of specificity signs and symptoms, it is difficult to reorganize it. Other than these, various factors cause increase in cancer incidence and prevalence. The cancer factors include environmental and genetic factors that cause cancerous cells with the damage and deficiency in genome operation. The studies have demonstrated that cancer incidence grows with age, and elderly people are more exposing to high-risk factors of hard curable diseases such as cancer. All of these factors are increasing in environment. Cancer-making genes observed in relation to stomach cancer are mostly specialized to P53 gene although other genes are also involved.<sup>[47]</sup> Among all stomach cancers, adenocarcinoma accounts for 95% of stomach malignancies and the rest 5% involve lymph, stromal and other rare tumors. Genetic, individual, environmental, and infectious factors are involved in stomach cancer. In addition, men are usually in double

risk of affliction in comparison with women. Stomach cancer is one of the digestive system cancers that due to its weak recognition, it is the second factor of death rate related to cancer.<sup>[48]</sup> Genetic factors, smoking, and chronic infections are the important factors, especially for stomach cancer. There are more than 100,000 chemical compounds that directly or indirectly have their effects and harms in cytoplasm and cell's nucleus and lead to genetic disorders and finally cause mutations. In addition, viruses, bacteria, and different radioactive make inherited cancer that their number is about 7% of all cancers.<sup>[49-51]</sup> In Table 1, some cancer symptoms are presented.<sup>[46]</sup> Some studies have mentioned the *Helicobacter pylori* and improper diet as the most important factors of stomach cancer.<sup>[52]</sup> Generally, the prevalence of *H. pylori* in developing countries is >80%, and in developed countries, it is <30%.<sup>[53]</sup> *H. pylori* is a little bacillary form bacteria that create infection in mucous layer of human stomach, and if the infection lasts, 10%–15% of people are afflicted to ulcers or/and stomach cancer.<sup>[51]</sup> The *Helicobacter* infection is a very important and effective factor in stomach cancer and distinguishes this cancer from other types of cancer.<sup>[52,53]</sup> In the last years before the recognition of this bacteria, it was specified that adenocarcinoma usually derived from the stomach. Scientists' viewpoints have changed the relationship of this bacterial infection with the risk of cancer creation in gastritis lesion location.<sup>[54]</sup> Generally, the *H. pylori* primary infection causes the creation of slight gastric, and in some people, this inflammation leads to stomach ulcers.<sup>[55,56]</sup> The presence of pathogenic factor and lack of stomach ulcers treatment cause the atrophic inflammation. People afflicted to this inflammation are in risk of malignancy and cancer.<sup>[55]</sup> Another risk factor is smoking. In a study that was done in 2007, it was recognized that stomach cancer in smokers was double in comparison with those who were not smoking.<sup>[57]</sup> Some other risk factors for this illness are fatness, salt, red meat, hot drinks, and pepperoni foods.<sup>[58-64]</sup> In conclusion, it might be said that different factors are determinative of stomach cancer incidence and the consideration of just one-factor increase or decrease cannot be recognized. In Table 2, some of the most important environmental factors related to stomach cancer and other cancers are presented.<sup>[46,47]</sup> The incidence rate of cancer is increasingly growing. This increase is significant in the west part of Iran and considers as a problem. This increase is observed in other parts of the country, too.<sup>[20]</sup> In addition, in studies performed in Iran, stomach cancer is reported higher for men than women. In west part of Iran,<sup>[19]</sup> the prevalence is 2.7; in Davoodabadi's study,<sup>[65]</sup> it is 2.8; in Safahi,<sup>[66]</sup> it is 2.3, and in Rajaeefard's study,<sup>[67]</sup> it is 2.2.

### The Anticancer Effect of Medicinal Plants and Their Effective Compounds

Nowadays, medicinal plants usage has gained attention because of their protective roles against damaging factors. These plants have an important role in community health.

**Table 1: Some syndromes of inherited cancers**

Syndrome	Cloned gene	Function	Chromosomal location	Tumor types
Li-Fraumeni syndrome	P53 = Tumor suppressor	Cell cycle regulation, apoptosis	17p13	Brain tumors, sarcomas, leukemia, breast cancer
Familial retinoblastoma	RB1 = Tumor suppressor	Cell cycle regulation	13q14	Retinoblastoma, osteogenic sarcoma
Wilm's tumor	WT1 = Tumor suppressor	Transcriptional regulation	11p13	Pediatric kidney cancer
Neurofibromatosis Type 1	NF1 = Tumor suppressor = Protein = Neurofibromin 1	Catalysis of RAS inactivation	17q11	Neurofibromas, sarcomas, gliomas
Neurofibromatosis Type 2	NF2 = Merlin also called neurofibromin 2	Linkage of cell membrane to cytoskeleton	22q12	Schwann cell tumors, astrocytomas, meningiomas, ependymomas
Familial adenomatous polyposis	APC = Tumor suppressor	Signaling through adhesion molecules to nucleus	5q21	Colon cancer
Tuberous sclerosis 1	TSC1 = Tumor suppressor protein = Hamartin	Forms complex with TSC2 protein, inhibits signaling to downstream effectors of mTOR	9q34	Seizures, mental retardation, facial angiofibromas
Familial breast cancer	BRCA2	Transcriptional regulation of genes involved in DNA repair and homologous	13q14	Breast and ovarian cancer

**Table 2: Some factors related to human cancers**

Carcinogens	Cancer sites	Occupational sources
Ethylene oxide	Blood	Ripening agent for fruits, rocket gases
Radon	Lung	Uranium decay, mines, cellars
Smoke	Lungs, colon	Air pollution
Formaldehyde	Nose, pharynx	Hospital/laboratory workers
Ionizing radiation	Bone marrow	Radiology technician
Hepatic virus-B, C	Liver	Hospital workers, drug users
HPV/herpes viruses	Cervix, skin, head/neck	Multiple sexual partners
Burkitt virus	Lymph node	Black people in South Africa
<i>Helicobacter pylori</i>	Stomach	People with chronic bacterial infection

HPV=Human papillomavirus

The application of these plants demonstrates the importance of their effective compounds to treat disease.<sup>[68-74]</sup> The secondary metabolites in plants are a lot, and lots of them are not still recognized. The plant compounds that have anticancer and antitumor features lay in aldehydes, alkaloids, flavonoids, glycosides, terpenoids, and phenol compounds. These compounds also have some other properties. It is significant that nowadays, >60% of common anticancer medicines are derived from natural resources including plants and microorganisms.<sup>[75]</sup> There are effective compounds with anticancer effect that might lead to cancer cells inhibition through the cell apoptosis increase. It has been found that phenol thymol compound dose-dependently has antioxidant effects on prostate cancer cells. The mechanism of these phenolic compounds is due to the oxidative stress reduction or due to the cyclooxygenase enzymes inhibition.<sup>[74]</sup> Photochemical existent in the essence of *Thymus kotschyanus*, especially the leaf, have antiseptic, antifungal and antioxidant activities. The flowered branches

of this plant are full of phenol compounds, especially thymol and carvacrol. The phenol and thymol compounds have the inhibitory effect on cyclooxygenase enzyme activity. These compounds and similar ones have a wide range of other properties.<sup>[76-80]</sup> With regard to the anticancer effect of effective thymol and carvacrol compounds, the application of *T. kotschyanus* plant and other plants with these compounds might be effective in cancer prevention and treatment. Other researches have demonstrated that hydroalcoholic extract of *Lagenaria siceraria* leaf has the toxicity effect on cancer cells levels of Hep-2, MCF-7, and A-549, because of having pectin, saponins, flavonoids, tannins, steroids, such as focostrol and campsrol, phenol compounds, and glycosides.<sup>[81]</sup> Barhang kabir (Great plantain) with scientific name of *Plantago major* L. belongs to *Plantaginaceae* family. It has several medicinal properties such as skin protection, cancer prevention, and tumor prevention.<sup>[82,83]</sup> Barhang kabir (*P. major* L.) is an important medicinal plant for cancer treatment that has compounds such as phenol compounds (caffeic acid derivatives), flavonoids, alkaloids, and terpenoids. The main flavonoid compound in *Plantago* species is the Luteolin 7-glucoside compound that has important role in cancer prevention.<sup>[82,83]</sup> Recently, there are many reports based on the *Plantago* species in traditional medicine against cancer in different countries around the world such as Mexico and Argentina.<sup>[84]</sup> *P. major* in the Canary Islands, Chile, Venezuela, and Panama are applied for tumor treatment.<sup>[85,86]</sup> Bedir et al. reported that steroids, saponins derived from *Tribulus terrestris*, destroy lines SK-Mel, KB, BT-459, and SK-OV-3.<sup>[87]</sup> In another study, Kim et al. (2011) reported that aqueous extract of *T. terrestris* fruit prevented the cells proliferation and inhibited apoptosis in liver cancer cells (HPGZ) through signaling NFkB in a dose-dependent manner.<sup>[88]</sup> The *Crocus sativus* has antiactivating leukemia and ovary cancer features.

Furthermore, the prevention of cancer cells activity for breast cancer by two types of *C. sativus* is confirmed.<sup>[89,90]</sup> Other studies have demonstrated that *C. sativus* extract in laboratory environment can prevent the formation of tumor cells and cell DNA and RNA formation through Hela cells. In addition, it is specified that *C. sativus* extract and combine crocins significantly inhibited the colorectal cell growth without effect on other cells growth.<sup>[91]</sup> The mechanism of plant medicinal plant effect on cell different lines is reported by researchers.<sup>[92]</sup> Gole-Mohammadi with scientific name of *Rosa damascena* from *Rosaceae* family contains carboxylic acid, myrcene, camphor, and quercetin.<sup>[93]</sup> The phenol compounds of Gole-Mohamadi (*R. damascena*) remove free radicals and the antioxidant effect of this plant has role in the prevention of cancer and destructive cancer cells through different paths such as apoptosis promotion and prevention from angiogenic and metastatic growth. The research demonstrated that ethanol and aqueous extract of *R. damascena* prevented the cell proliferation of AGS level (the stomach and carcinoma).<sup>[94,95]</sup> This effect is related to the plant antioxidant compounds. Antioxidant compounds such as phenols, polyphenols, and flavonoids scavenge free radicals such as peroxide or hydroperoxide and prevent the oxidative process that leads to genome damage and mutation incidence.<sup>[96-100]</sup> Star thistle plant with scientific name of *T. terrestris* in traditional medicine is used for several diseases treatment such as cancer.<sup>[101]</sup> The extract of this plant and some other plants contain saponins, alkaloids, flavonoids, and sterol.<sup>[102-103]</sup> Star thistle causes the inhibition of cancerous cells AGS level. Saffron with the scientific name of *C. sativus* has anticancer effects, and in dry saffron stigma, more than 150 compound composition has been recognized such as glucose, minerals, and secondary metabolism, including terpinenes, flavonoids,

anthocyanin, and carotenoids.<sup>[95]</sup> *C. sativus* extract postpones the tumor activity in mouse.<sup>[96,97]</sup> Several researches have shown the cytotoxic effect of saffron (*C. sativus*) extract on cancer cells *in vitro*.<sup>[98-100]</sup> The exposure of cancerous cells in saffron extract causes the acid nucleic synthesis in cells.<sup>[101]</sup> The results of research have confirmed that this plant extract causes inhibition of cancer cells AGS level.<sup>[102-106]</sup> Table 3 refers the most important medicinal plants with anticancer of different lines such as AG (stomach adenocarcinoma).

## Conclusions

Nowadays, cancer is the most important problem and the number of afflicted people to this disease is increasing fast. The cancer common treatments often destroy healthy cells that cause the toxicity effects and subsidiary effects on patients. Therefore, today, there is an inclination toward the use of plants and their compounds as potential anticancer that has direct toxic activities on malignant cells. Since stomach cancer is considered as one of the most important dead factors around the world, the application of medicinal plants and their effective compounds, as low-risk natural factors with the highest anticancer effects and the least subsidiary problems, have a special importance.

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**Table 3: The medicinal plants and their effective compounds in cancerous line inhibition**

Scientific name	Persian name	Plant species	Anticancer compounds	Cancerous level	Source
<i>Rosa damascena</i>	Gole-Mohammadi	<i>Rosaceae</i>	Quercetin, camphor, geraniol	AGS, MCF-7	[94]
<i>Thymus kotschyianus</i>	Avishan koohi	<i>Lamiaceae</i>	Thymol, carvacrol	A-549	[113]
<i>Lagenaria siceraria</i>	Kadu ghaliiae leaf plant	<i>Cucurbitaceae</i>	Phocostrol, compserol, saponins	Hep-2, MCF-7, A-549	[81]
<i>Tribulus terrestris</i>	Star thistle	<i>Zygophyllaceae</i>	Steroids saponins, flavonoids, alkaloids, sterol, phenol compounds	AGS, SK-MEL, KB, BT-549, SK-OV-3, HPG2	[103]
<i>Crocus sativus</i>	Saffron	<i>Iridaceae</i>	Carotenoids, monoterpenes, aldehydes, crocetin, crocins, safranin, picrocrocin	MCF7, HePG2, HeLa, H29, TC1, L929, AGS, TCA8113, HCT-116, SK-OV 3, SW480, HL 60, HT125	[88,107,113]
<i>Plantago major</i>	Barhang kabir	<i>Plantaginaceae</i>	Caffeic acid, flavonoids, alkaloids, terpenoids	MCF-7, UACC-62	[83,84]
<i>Artemisia absinthium</i>	Afsentin	<i>Asteraceae</i>	Artemisinin, quercetin, isorhamnetin, camphor, alpha-pinene, saponins, Germacrene-D	HeLa, HT-29, MCF7	[95,114,115]
<i>Cichorium intybus</i>	Kasni	Composite	Lacton sescoetrepens	C32, Jurkat	[118,121]
<i>Salvia officinalis</i>	Maryam goli	<i>Lamiaceae</i>	Alpha-terpineol, Beta-pinene, cineole, monoterpenes-thujene	HeLa, MCF-7, HT-29	[122-125]
<i>Silybum marianum</i>	Khar maryam	<i>Asteraceae</i>	Silymarins	MCF-7, SGC 7901, HT-29, A549	[126-129]

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