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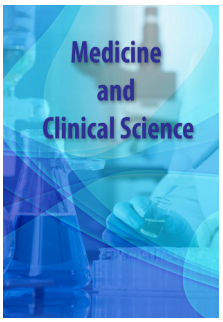

Correction of Cancer Medication With Herbal Preparations

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Abstract

Nowadays cancer chemotherapy includes antibiotics, antimetabolites, alkylates, topoisomerase inhibitors and mitotic inhibitors, hormones. The search for medicinal plants that can prophylactically prevent or at least slow down the homeostasis disturbance is especially relevant. To date, the most widely used for the body restoring plant is licorice. By reducing the oxidative stress, licorice components contribute to the restoration of vitality of non-cancer cells. With a multifaceted effect on receptor-mediated signaling, pro- and anti-inflammatory processes, licorice compounds are drugs of choice to eliminate adverse reactions after cancer chemotherapy. This herb has long been used in the East as an adjuvant for adverse reactions. In this article, we discuss the main mechanism of anticancer drugs action along with the protective properties of licorice.

Conclusion: *Licorice reduces the symptoms of mucositis, anorexia, chronic fatigue during cancer treatment, has a hepatoprotective effect, helps to restore the immune cells activity.*

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Keywords

Cancer; chemotherapy; licorice; receptors; adverse effect

İntroduction

The main reason of scanty cancer cases in the past

Cancer continues to be a major health problem worldwide, and the search for new but safe compounds for prevention and treatment is a top priority. Cancer is one of the main causes of planet working- age population death in all countries. İn 2017, almost half (46% of all people who die from cancer) are people aged 70 and over. Lung cancer is leading, and smoking is largely to blame. A decrease in the proportion of smokers also reduces mortality from lung cancer. Along with that, cancer survival rates are often much lower in poorer countries [1]. İn 2018, cancer accounted for about 9.6 million deaths and is expected to increase by 2025 [2]. Physicians and scholars such as Avicenna (980–1037), Rhazes (965–915), Al-Zahrawi (936–1013) and Ibn al-Nafis (1218–1288) suggested both preventive and curative remedies to alleviate suffering, improve the quality of life for cancer patients. Referring to the prevention of cancer, Avicenna quoted: "As regards the prevention of its (cancer's) progression, this can be achieved by improving the diet and strengthening the affected organ with known effective drugs". Nigella Sativa (Black Seeds) of the Ranunculaceae family is one of the most commonly used medicinal plants throughout the Middle East [3]. The reason for less incidence of cancer in these countries is the Prophetic medicine predicting that black cumin seeds cure majority of diseases. So, the Prophet said about Nigella sativa (black seed): “Hold on (using this seed regularly)! Because it is a remedy for all diseases except death.” [4]. When the world's population moved away from natural plant healing resources, an increase in the incidence of cancer became inevitable. So, in 2020, more than 19 million new cases of cancer were registered, with statistics of 10 million deaths [5]. Currently, the East is also moving away from the Prophetic medicine, and this has a deplorable effect on the figures for the tumor growth: cancer cases are increasing at an alarming rate, so that by 2030 the incidence of cancer is expected to increase by 1.8 times [2].

The current state of cancer medicine

The current state of cancer medicine leaves much to be desired. So, after searching various databases (Cochrane Upper Gastrointestinal and Pancreatic Group Trial Registry, Cochrane Library, MEDLINE, EMBASE, Allied and Complementary Medicines Database, China National Knowledge Infrastructure, VIP Database, Wanfang Database and controlled trials of the Chinese Cochrane Center, on the Internet) Chen X et al. found no evidence to determine whether traditional Chinese methods is an effective treatment for some cancer types

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[6]. To evaluate the effectiveness and possible side effects of adding Chinese herbal medicines to radiation or chemotherapy for esophageal cancer, randomized controlled trials were conducted by Wei X et al., and the results showed that there is no evidence of the effectiveness of traditional medicine in the treatment of esophageal cancer [7]. Active research is underway to find more effective ways to treat tumors, or at least reduce side effects when using traditional methods of treatment. So, Jihan H. et al.identified biologically active components in huachansu (toad venom), as well as multiple targets and pathways of action of toad venom against hepatocellular carcinoma [8].

Standard cancer treatment

Traditional Antineoplastic Strategy

Chemotherapy includes anti-cancer antibiotics, antimetabolites, alkylates together with Nitrosoureas, topoisomerase inhibitors and mitotic inhibitors, hormones (corticosteroids), as well as immunostimulants and representatives of different groups, such as vitamins, trace elements and enzymes [9]. Standard chemotherapy works with the cell cycle at different phases of the cycle, since cancer cells form new cells faster than normal cells. Although chemotherapy drugs primarily damage cancer cells, they cannot distinguish them from healthy ones, which causes side effects. Each course of chemotherapy requires a very careful choice of balance in the dose of the drug to kill cancer cells while maximizing the preservation of normal cells. All chemotherapy drugs can be grouped according to the mechanism of action and chemical structure. Anti-cancer antibiotics change the DNA of cancer cells, for example anthracyclines interfere with replication, stop DNA copying during the cell cycle before dividing. Simultaneously, they bind to cancer DNA, so it cannot create copies of itself, and tumor proliferation is inhibited. A combination of checkpoint kinase inhibitors and DNA-damaging chemotherapy drugs can effectively kill tumor cells. For example, the ATP analog indocarbazole UCN-01 can inhibit checkpoint kinase 1, thus increasing the sensitivity of tumor cells to the antiproliferative effects of chemotherapy. Reverse Hoogsteen Polypurine Hairpins (PPRH) are used as inhibitors of checkpoint kinase 1 in combination with DNA damaging drugs demonstrating a synergistic effect [10]. Antimetabolites replace the normal building blocks of RNA and DNA, causing DNA to lose its ability to replicate and the cell cycle to stop. They are structural analogues of either purine and pyrimidine bases or folate cofactors involved in the synthesis of purines and pyrimidines. Some antimetabolites can insert into nucleic acids, causing structural abnormalities leading to DNA breaks [11]. Drugs aimed at stopping the production of the hormone prevent the binding of the hormone necessary for the growth of cancer cells, preventing their division and proliferation. Thus, antiestrogens are effective in reducing the growth of hormone-dependent breast cancer. They inhibit estrogen stimulation of several specific protein synthetic activities in breast cancer cells, including an increase in plasminogen activator activity, progesterone receptor levels, and the production of several secreted glycoproteins and intracellular proteins. However, antiestrogens do not interfere with the synthesis of estrogen receptors, do not accelerate or block the degradation of estrogen receptors, since the analyzes indicate that the receptor occupied by the antiestrogen degrades at a rate (t 1/2 = 4 h), that is, similar to the control unoccupied receptor [12]. Immunotherapy boosts the body's immune defenses by helping the patient's immune system recognize and attack cancer cells [13]. Immunotherapy is used to stimulate CD8+ T cells for further differentiation into cytotoxic T lymphocytes, as well as CD4+ T cells to mature into secreting interferon-γ T helper 1. As a result, the conveyor mechanism of activation of CD8+ cells, natural killers, granulocytes, macrophages directly destroying tumor cells is launched [14]. New era drugs in this context are antimicrobial peptides, which are part of innate immunity, recognize cancer cells by their negative charge, which is different from the charge of normal cells, and coalesce into diseased cells, followed by the formation of pores in them leading to necrosis / apoptosis. The electrostatic attraction between the negatively charged components of pathogenic, for example, bacterial and cancer cells, - on the one hand, and the positively charged AMPs, - on the other hand, plays an important role in the strong binding and selective destruction of bacterial and cancer cells membranes [15]. All-trans retinoic acid, Arsenic trioxide and asparaginase are an example of preparations of derivatives of vitamins, trace elements and enzymes used in cancer treatment [16,17].

Alkylating agents cause cytotoxic DNA damage, and this is their main mechanism of action. Cellular pathways such as DNA damage reversal, base excision repair, and mismatch repair respond to alkylation damage to protect against alkylation-induced cell death or mutation [18]. The task of the therapist is to block the recovery of cells mutated by the tumor while simultaneously protecting the healthy cells of the patient. And it is practically impossible to make this magic move without the support of plant components that simultaneously have immunomodulatory (stimulating immunity against diseased cells) and anti-inflammatory (suppressing the immune response against healthy cells). Licorice is just such a plant with mutually expressed properties. Nitroureas differ from alkylating agents in that they do not enter the brain, while nitroureas can because they pass through the blood-

brain barrier. Nitrosourea derivatives are more often used in chronic myelocytic leukemia, malignant lymphoma and small cell lung cancer, less often in cancer of the gastrointestinal tract, multiple myeloma and malignant melanoma. At physiological pH, chloroethylnitrosoureas can decompose into isocyanate and 2-chloroethyldiazene hydroxide, resulting in both alkylating and carbamoylating effects. Fat-soluble nitrosoureas and some water-soluble nitrosoureas can cross the blood-brain barrier, making them suitable for the treatment of primary brain tumors as well as tumors of metastatic origin. However, DNA alkylation with these drugs is slower than with other alkylating agents [19]. A relatively new class of drugs in the fight against tumors are topoisomerase inhibitors, or plant alkaloids interacting with topoisomerases, which normally determine the origin of replication to separate the DNA double helix to form a replication fork [20]. Topoisomerase inhibitors are grouped according to the type of enzyme they act on, as inhibitors of topoisomerase I and topoisomerase II. Topoisomerase I inhibitors are also called camptothecins. Nuclear DNA topoisomerase I is the only known target of the alkaloid camptothecin, from which the potent anti-cancer agents irinotecan and topotecan are derived. Since camptothecins bind to the surface of the DNA topoisomerase I complex, they reversibly trap macromolecular complexes preventing DNA replication [21]. Topoisomerase II inhibitors are called epipodophyllotoxins. Topoisomerase II inhibitor etoposide is an important chemotherapeutic agent whose main cytotoxic target is topoisomerase II, which regulates DNA under- and twisting and removes knots and tangles from the genome, creating temporary double-strand breaks in the double helix. İt converts topoisomerase II into a powerful

genome-fragmenting cellular toxin [22]. Mitotic inhibitors are plant alkaloids that stop cancer cells from dividing, they can damage cells at all stages. Examples of mitotic inhibitors include taxanes and vinca alkaloids. Vinca alkaloids and taxanes act to inhibit spindle microtubule dynamics (but not microtubule polymer mass) stopping cell cycle progression during mitosis, culminating in cell apoptosis. Side effects of this group of drugs include neurological and hematological toxicity, and an undesirable effect is also drug resistance, which also manifests itself in many other chemotherapeutic agents against cancer [23]. Corticosteroids help stop DNA replication and the transcription process in many peripheral cells, ultimately causing translational inhibition with subsequent tissue destruction, sometimes even tissue necrosis. For instance, dexamethasone, are potent pro-apoptotic properties in lymphoid cells that are used in cancer treatment while attenuating acute toxic effects in healthy tissues. Dexamethasone acts to enhance the cytotoxic effect of chemotherapy in established and primary lymphoid cells, however, it inhibits apoptosis induced by cisplatin and 5-fluorouracil and promotes the growth of most malignant cells studied [24]. Randomized controlled trials comparing cauterization treatment have shown that cauterization may also be an alternative or an aid in the tumor treatment [25].

Cancer Treatment Adverse Reactions

Since standard cancer treatments include cytotoxic chemotherapy, cured patients inevitably experience side effects sometimes as deadly as the tumor itself. So, chemotherapy-induced side effects include fatigue, anemia, constipation, chronic pain, oral mucositis, anorexia, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, insomnia, edema, anxiety/depression [26,27].

In a study of 2406 participants on the risk of cognitive impairment after radiotherapy, it was found to be higher in the radiotherapy group compared to controls [28]. A decrease in the number of blood cells during chemotherapy leads to an artificial interruption of treatment, which ends badly and even fatally for the patient. Therefore, it is important to develop more effective therapeutic treatment strategies to reduce the toxicity of chemotherapy.

Necessity for effective therapeutic approaches to cancer treatment

Herbal Composition Most Commonly Prescribed in Medicine

The sharp increase in the prevalence of cancer and the ineffectiveness of modern drugs indicate the need for the introduction of novel effective therapeutic approaches [29]. Processing of 96,000 recipes by Microsoft SQL Server 2000 showed that licorice (Radix glycyrrhizae) was the most commonly used herb in China, and the top three herbs (the toxic herbs Radix aconiti lateralis praeparata, Rhizoma pinelliae and Cinnabaris) were most commonly used in combination with licorice. The three most commonly used non-toxic herbs (Radix et rhizoma ginseng, Poria and Radix Angelicae Sinensis) are also commonly recommended in combination with licorice [30]. Licorice belongs to the genus Glycyrrhiza, the most valuable material of which are dried roots and rhizomes; the active component glycyrrhizin is more available in thick roots and rhizomes than in thin parts [31]. Licorice is used as painkiller, to increase phlegm in dry coughs, spasm relief, relieve cough and eliminate shortness of breath. More than 300 biologically active compounds have been identified in licorice, among which the most valuable are the main components and biologically active ingredients are flavonoids [32,33], (mainly liquiritin (LT), liquiritigenin (LTG), and isoliquiritin (ILT) [34]. The content of ILT, LTG, and LT in G. uralensis is higher than in G. glabra, while glycycoumarin is present only in G. uralensis [35]. Glycyrrhizin is nearly evenly distributed among different licorice species. ILG is higher in G. uralensis than in both G. glabra and G. inflata [36]. Research results indicate that flavonoids from Glycyrrhiza uralensis licurazide, isoliquiritin and licochalcone A have high potential as effective anti-darkening and depigmentation agents [34]. Pre-incubation with glycyrrhizin (0.8 mM for 12 h) in H9c2 cells protected against Doxorubicin-induced cytotoxicity, oxidative stress, and mitochondrial membrane potential depolarization. Glycyrrhizin reverses the induced by the anti-cancer chemical, doxorubicin expression of LC3 II and and a ubiquitin-associated protein p62, and improves impeded autophagy flow in H9c2 cells. Glycyrrhizin was found to suppress a major intracellular path leading to cell proliferation: Akt/mTOR autophagy signaling pathway in H9c2 cells. In addition, glycyrrhizin significantly downregulates the expression of phospho-Akt and phospho-mTOR (mTOR, a mammalian target for rapamycin plays a crucial role in cell growth). Glycyrrhizin impacts activity of the high-mobility group protein B1 (HMGB1), amphoterin, which is a non-histone protein that interacts with a nuclear DNA. The results suggest that glycyrrhizin -enhanced autophagy flux through the HMGB1-dependent Akt/mTOR signaling pathway may help attenuate toxicity of anticancer drugs [37].

Benefits of Licorice Hepatoprotective Properties for Cancer Treatment

The main organ responsible for detoxifying the body and restoring its vital functions is the liver. Any slowdown in its work immediately affects the state of the immune system responsible for the removal of threatening toxins and maintaining immunity, removing both cancer cells and toxins accumulated during chemotherapy and radiation treatment. For this reason, the hepatoprotective properties of licorice in the treatment of cancer patients cannot be overestimated. The non-toxicity of drugs developed on the basis of medicinal plants is the reason for focusing on the effect of a very affordable plant, licorice, on the cancer patients undergoing treatment with chemotherapy drugs (Figure 1).

Glycyrrhizin from licorice has long been used in liver disease [37]. First the antihepatotoxic effect of licorice extract was revealed in case of liver damage caused by carbon tetrachloride, CCl4. Licorice extract significantly inhibited the increased activity of aspartate amine transferase (AST), alkaline phosphatase (ALP) and alanine amine transferase (ALT) and the decrease in total protein, serum albumin and globulin levels caused by CCl4 intoxication. İt also increases the activity of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, and glutathione levels, while decreasing hepatic malondialdehyde levels. Licorice extract also significantly reduces serum tumor necrosis factor (TNF-α), which proves that licorice extract substantially eliminates manifestations of oxidative liver damage [38]. The combination of glycyrrhizin and ciclosporin A to reduce ciclosporin-related liver side effects in the treatment of patients with aplastic anemia has shown that the addition of glycyrrhizin to ciclosporin A significantly reduces liver damage.

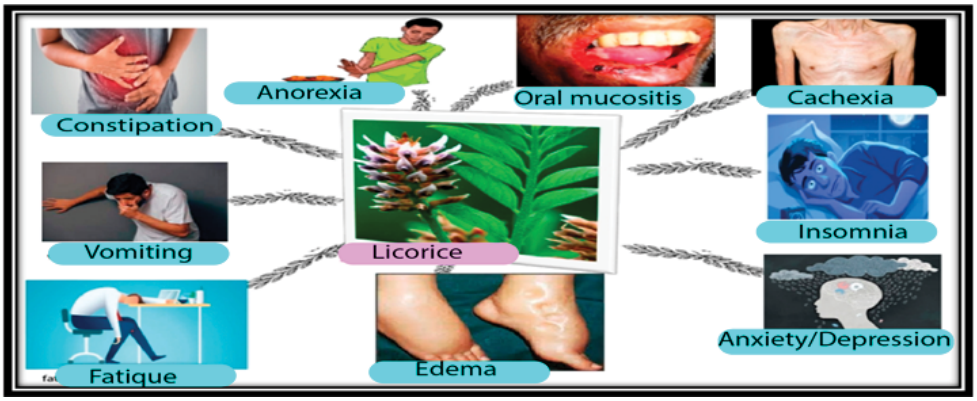

***Figure 1**. The points of Licorice restorative properties application*

Other Beneficial Properties of Licorice

Licorice extract also acts as a moderate hypocholesterolemic nutrient and a powerful antioxidant to prevent cardiovascular disease [39]. Licorice can also prevent dyspepsia and hyperlipidemia [40]; simultaneously with a glycyrrhizin-containing product, licorice exerts a hepatoprotective effect in drunks [41].

Well-tolerated treatment to eliminate the side effect caused by cyclosporine A indicating a good safety profile use of glycyrrhizin [42]. Preoperative gargling with licorice solution reduces postoperative sore throat. There are claims that licorice-containing drugs in combination with chemotherapy can potentially reduce the side effects of chemotherapy drugs such as mucositis, anemia, anorexia, and fatigue, and they cost much less than traditional medicines [43].

Licorice (Glycyrrhiza) and its derivatives exert antioxidant, anti-inflammatory effects; involving in detoxification, it exhibits anti-infective activity and anti-cancer effects indicating their potential as chemopreventive or therapeutic agents [38]. For example, licorice can be used to reduce inflammation and allergic reactions, and to prevent liver damage. It is believed that the anti-cancer activity of licorice is based on cell cycle arrest, induction of cancer cell apoptosis and strengthening the body through antioxidant action. Thus, there are reports on the effect of licorice components on proteins associated with the cell cycle or apoptosis, kinases of Cyclooxygenase COX-2, glycogen synthase kinase (GSK-β), serine/threonine-protein kinase Akt, nuclear factor kappa (NF-κB) and mitogen activated protein (MAP), as well as gene MKK4 encoding MAP4, on the ability to directly bind and inhibit the activity of Phosphoinositide 3-kinase (PI3-K), MKK7 , JNK1 encoding MAP kinase, mammalian target of rapamycin (mTOR), and cyclin-dependent kinase 2, (Cdk2), leading to a reduction in carcinogenesis in several cell models without causing signs of toxicity [44].

Achievements in the Correction of Cancer Medication with Herbal Preparations.

It has recently become known that a licorice-based medicine can be combined with chemotherapy to reduce side effects such as fatigue, anorexia, mucositis and anemia, alleviates gastrointestinal problems caused by anorexia and chemotherapy. Licorice is used for peptic ulcers, hepatitis C, lung and skin diseases [45]. The flavonoids and triterpenoids present in licorice root are the main biologically active compounds of the plant, so LT from licorice is the main active component that exerts a laxative effect and relieves constipation [40,46]. Licorice is effective in vomiting and nausea highly relevant in tumors [43]. Along with this, mediating the secretion of pro-inflammatory cytokines (interleukine IL-6 and chemokine C-X-C motif ligand 8 (CXCL8) and enzymes of the matrix metalloproteinase MMP-1 and MMP-9 decomposing damaged tissues [47], licorice-derived agent is prescribed to treat fatigue, visceroptosis, and chronic diarrhea. When used with cisplatin, licorice-based remedies improve chemosensitivity and inflammation, help in cancer-related cachexia, anorexia and fatigue [48]. Finally, the licorice-based preparations help to achieve a balance between pro-inflammatory and anti-inflammatory processes in the body suffering from a tumor, since it also shows an anti-inflammatory effect inhibiting proinflammatory cytokine IL-6 production [49]. For instance, inhibiting the production of mitochondrial reactive oxygen species, licorice based remedies inhibit chemotherapy-induced apoptosis [49], and this phenomenon can be used in the treatment after chemotherapy to restore non-specifically damaged cells. It also strengthens the peripheral immunity suppressing the escape of tumors from immune recognition [43].

Additionally, the Licorice triterpenoid saponin, glycyrrhizic acid, exhibits the mucoprotective, anti-inflammatory and antioxidant effects [50]. It suppresses inflammatory mediators and oxidative stress via nuclear factor kappa B (NF-κB) and Nrf2 pathway that enhances pentose phosphate pathway in cancers resulting in their growth, acts as a nitric oxide regulator decreasing the expression of multidrug resistance-associated proteins MRP2, MRP3, MRP4, and MRP5 along with inhibition of HMGB1, it increases chemosensitivity during chemotherapy [37,51,52].

To date, triterpene saponin Glycyrrhizin (GL) and chalcone isoliquiritigenin (İLG) are representative components of Glycyrrhiza uralensis that attenuate Toll-like receptor (TLR)-mediated inflammatory responses thus improving the immune system state in cancer patients. GL and ILG inhibit various steps in bacterial lipopolysaccharide-responsive TLR4/MD-2 receptor signaling. Thus, Glycyrrhiza uralensis extract suppresses the production of IL-6 and tumor necrosis factor-α (TNF-α) induced by the fragment of lipid lipopolysaccharide A in cells. In addition, the increase in TNF-α levels under the action of bacterial lipopolysaccharide is attenuated by passive administration of GL or ILG. GL and ILG also inhibit lipid

A-induced NF-kB activation in cells expressing TLR4/MD-2, claster of differentiation CD14. These components inhibit the major mitogen-activated protein kinases (MAPK) activation: c-JUN N-terminal kinase (JNK), p38, and extracellular signal-regulated kinase (ERK) that regulate apoptosis [53]. In addition, GL and ILG inhibit NF-kB activation and IL-6 production induced by the non-bacterial TLR4 ligand. Although ILH does not affect the binding of lipopolysaccharide to TLR4/MD-2, but GL weakens the formation of lipopolysaccharide-TLR4/MD-2 complexes, which leads to inhibition of TLR4 homodimerization [54]. All these effects serve to protect self cells from foreign ones and weaken the hyperactivation of the inflammatory process leading to the normalization of cancer patients life quality.

Conflict of Interests

Authors have no conflicts of interest to disclose.

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