

Use of Herbal Products and Complementary and Alternative Medicine (CAM) During Pregnancy

Gebelik Döneminde Bitkisel Ürünler ve Tamamlayıcı/Alternatif Tıp (TAT) Kullanım

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ABSTRACT

Ideal nutrition for all stages of pregnancy is so important, and the safety of consuming common foods, herbal products, complementary and alternative medicine (CAM), and nonnutritive substances is questionable. Despite the fact that herbs are entirely natural, not all of them are safe to ingest during pregnancy. Herbs such as ginger and peppermint are well known for being a powerful, safe, and effective remedy for vomiting and nausea during pregnancy. Pre-eclampsia and high blood pressure are among the important complications during pregnancy. Pre-eclampsia could be increased by drinking tea, while high blood pressure could be decreased with garlic consumption in pregnant women. During pregnancy blood glucose levels and glycogen storage are as important as blood pressure. Turmeric controls blood glucose levels, meanwhile red pepper enhances glycogen storage. Interacting with the cytochrome P450 system causes many food-drug interactions. St. John's Wort is one of the commonly used herbs that affects this system and should be taken cautiously in pregnancy. Chamomile should be consumed cautiously as well due to its effects on individuals suffering from coagulation disorders. As a safe herb during breastfeeding, fennel should be consumed wisely in pregnancy. Fennel contains estrogen-like features that affect fetal development and birth weight. As herbal products have varying and ambiguous effects, they should be consumed (as condiments, flavoring in foods or beverages) prudently.

Keywords: : Herbs, Complementary and Alternative Medicine (CAM), Pregnancy

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Ö Z E T

İdeal beslenme hamileliğin tüm evrelerinde çok önemlidir. Bununla birlikte, tüketilen tüm yaygın gıdalar, bitkisel ürünler, tamamlayıcı ve alternatif tıp (TAT) ve besleyici değeri olmayan maddelerin güvenilirliği tartışılabilir. Bitkiler her ne kadar doğal olsalar da, hamilelik sırasında tüm bitkilerin tüketimi güvenli olmayabilir. Zencefil ve nane gibi bitkiler, hamilelik döneminde en sık dördüncü ile altıncı haftaları arasında görülen gebelik kusma ve bulantıları için güçlü, güvenli ve etkili tedavi olarak tanımlanırlar. Preeklampsi ve yüksek tansiyon önemli gebelik komplikasyonları arasında yer alır. Hamile kadınlarda çay içmek preeklampsi riskini artırabilirken, sarımsak tüketimi ile yüksek tansiyon düşürülebilir. Hamilelik sürecinde kan şekeri seviyesi ve glikojen depolanması en az kan basıncı kadar önem taşımaktadır. Zerdeçal, kan şekeri seviyesini düzenleyip kontrol ederken kırmızı biber vücutta glikojenin depolanmasını artırır. Sitokrom P450 sistemi ile etkileşim, birçok gıda-ilaç etkileşimine yol açar. Bu sistemi etkileyen ve yaygın olarak kullanılan bitkilerden biri olan sarı kantaronun hamilelik döneminde dikkatli alınması gerekir. Hamilelik döneminde tüketiminde ihtiyatlı olunması gereken bir diğer bitki de papatya'dır. Papatya yan etkileri sebebiyle pıhtılaşma bozukluğu olan bireyler tarafından dikkatli tüketilmelidir. Rezene emzirme döneminde güvenli bir bitki olarak tanımlansa da, hamilelikte bilinçli ve akıllıca kullanılmalıdır. Rezene östrojen benzeri özellikler içerdiğinden, hamilelik döneminde fetal gelişimi ve doğum ağırlığını etkileyebilir. Bitkisel ürünler değişken ve belirsiz etkiler gösterebildiği için çöşni, tatlandırıcı veya içecekler olarak dikkatli tüketilmelidir.

Anahtar Kelimeler: Bitkiler, Tamamlayıcı ve Alternatif Tıp (TAT), Gebelik



1. Introduction

İdeal nutrition for all stages of pregnancy, including enough amounts of all needed vitamins, minerals, and energy-supplying macronutrients, should begin before conception. During these times, fetuses' developing status depends exclusively on the transfer of substrates from their host, because any other pathways are not possible to obtain in utero [1]. The risk of pregnant women's exposure to pathogens is very close to non-pregnant individuals, but the adverse consequences of exposure to foodborne illnesses for both mother and fetus remain important. Moreover, during pregnancy, metabolically active tissues may be more vulnerable to the action of toxins, which increases the importance of acquaintance or intake and, along with the potential long-term effects of fetal exposure to suboptimal conditions, the safety of common foods and nonnutritive substances is questioned. Those food safety issues of most concern vary between populations [1-3].

On the other hand, there is a growing trend among the public – including pregnant women – to use alternative and/or herbal medications and supplements that are thought to offer potential health benefits, as well as a widespread belief that natural goods are safe [4]. Many people assume that herbs are typically better, cheaper, and healthier than their medical counterparts. Many medical experts, on the other hand, do not advocate herbal medicines for pregnant women because their safety has not been verified via thorough research. But still it is common to use complementary and alternative medicine (CAM) during pregnancy all over the world [5].

Although herbs are entirely natural, not all of them are safe to ingest during pregnancy. The FDA advises pregnant women not to consume any herbal products without first consulting their healthcare professional [5-7]. The growing prevalence of herbal medications taken during pregnancy in recent years, as well as the lack of knowledge about the safety of these treatments, has become a public issue. Despite this, research has conducted on the potential negative effects of utilizing herbal medicines during pregnancy, particularly in impoverished Asian countries [8].

As discussed above, there is an enormous use of CAMs by pregnant women because of these remedies' possible benefits. Women can use herbal remedies during pregnancy for a variety of reasons, according to studies. Nausea/vomiting, abdominal pain, preventing neonatal hyperbilirubinemia, breathing issues, as a relaxant, to aid labor, and to improve neonate intellect are among the most common indications [9-10].

The most investigated CAM herbs are: Ginger, tea/green tea, peppermint, St. John's Wort, fennel, pepper and garlic are among these choices. The benefits of these products still remain in contradiction, with their possible food-food or herb-drug interactions and their potential clinical significance in this group [11]. In this review, we tried to indicate some of the well-known and most common herbs (used as condiments, flavoring in foods or beverages in Turkey) and their effects on pregnant women.

Herbal products, CAM, and pregnancy

Ginger:

Nausea and vomiting are two of the most prevalent side effects of pregnancy. Pregnancy-induced nausea and vomiting (PNV) is most frequent between four and six weeks following conception, but it can develop as soon as two to three weeks after the last menstrual cycle begins. Symptoms peak between eight and twelve weeks and then fade away between three to four months. Symptoms can last for fourteen weeks in 40% of women, and even sixteen or twenty weeks in uncommon cases. In many cultures, this problem is known as morning sickness and affects roughly 80-90 percent of pregnant women to variable degrees [12-13].

Many women prefer not to employ typical medical treatments because of the possible detrimental side effects that traditional drugs may have on the unborn fetus. They are not entirely incorrect, as several physiological changes occur during pregnancy, such as alterations in gastrointestinal motility, plasma volume, and glomerular filtration. On the other hand, for many years, ginger has been the most extensively utilized herbal medicine in the treatment of PNV, and the interest in this well-known herb/spice has been rising in recent years [13-14].

Native to many Asian countries, ginger has been a popular remedy for thousands of years. Ginger's effects, such as anti-emetic, and anti-inflammatory effects, and its ability to stimulate digestion, make it common in many traditional medicines. However, we should not forget these herbs' significant side effects, including anticoagulation effect. Ginger - known as a significant, safe and effective treatment for PNV - has been indicated in some studies that is even more effective than vitamin B6 (which is the used choice medicine for PNV), for some symptoms of PNV in a safe range [15].

Furthermore, ginger extracts, 6-gingerols and 6-shogaol, have shown significant free-radical scavenging role; they inhibited the synthesis of inflammatory mediators, as well as the activity of inflammatory cytokines. Throughout *in vitro* investigations, it also suppressed COX-2 [16].

As proven in clinical trials, 1 g/day intake of ginger would be safe and effective against PNV. Yet, individuals should be cautious while taking ginger, because the upper limit for intake is 4 g/day. Daily ginger intakes of more than 4 g may cause adverse effects and concerns during pregnancy. As well, high doses of this herb may be involved in aggravating pre-existing circumstances, such as cholelithiasis, or contributing to cardiac arrhythmia, depression of the central nervous system, and heartburn [12, 16].

Green tea:

As a well-known drink in many countries, as well as Turkey, people, not only for pleasure, but also for their benefits, use different kinds of tea all around the world. Epigallocatechin gallate (EGCG), the most prevalent flavonoid type in green tea, thought to provide considerable health advantages in both the prevention and treatment of chronic diseases. The preventive effect of green tea on the neurodevelopmental adverse effects was also shown in a preclinical study [17].

On the other hand, one of the most common complications during pregnancy is preeclampsia, described by high blood pressure plus symptoms of damage to another organ system, most commonly the liver

and kidneys. This complication usually appears after 20 weeks of pregnancy in pregnant women who had previously had normal blood pressure. However, it sometimes develops without causing any symptoms, or high blood pressure can increase slowly or suddenly. In the prenatal care issues, the most important factor according to preeclampsia, would be blood pressure monitoring, since usually, the first indication of it is an increase in blood pressure [18].

Unlike other hypertension-related diseases, preeclampsia patients could not use routine medical treatments in case of being unsafe during pregnancy. However, nifedipine is one of the few available options. Along with this, EGCG of green tea is reported to be safe and effective for numerous pregnancy-related complications. Furthermore, EGCG has therapeutic efficacy and safety in enhancing the efficacy of nifedipine in patients with pregnancy-induced severe pre-eclampsia [19].

It was also illustrated a statistically significant association between tea consumption and an increase in the risk of hypertension (PIH) caused during pregnancy. One of the possible mechanisms for clarifying this could be due to the presence of components elevating homocysteine levels, such as polyphenol chlorogenic acid and caffeine in tea. Too high levels of homocysteine are linked to an increased risk of PIH and preeclampsia [20].

Likewise, bioactive components found in tea, especially green tea, have shown antioxidative roles. This reduces fat deposits and body bulk while increasing fat oxidation, insulin activity, energy expenditure, and metabolism. An *in vitro* study on rats showed that green tea extract intake during pregnancy had a preventive function against dyslipidemia and glucose intolerance. Nonetheless, ingestion of green tea extract during this period affected on the offspring's metabolic development via altering metabolic programming [21].

Conversely, studies are elucidating another possible pathway in which tea consumption considerably connected to a higher risk for pre-eclampsia. They attributed the effects of green tea to possibly flavonoids rather than caffeine. Recent studies have demonstrated an increased oxidative stress effect along with anti-oxidant effects of flavonoids, also a type of polyphenol. Overall, tea's influence on blood pressure during pregnancy is still controversial [20, 22].

Garlic:

Garlic, like tea and ginger, has a long history of use in traditional medicine several ailments, including the prevention and treatment of colds, bronchitis, dysentery, influenza, gastroenteritis, and skin disorders. In recent years, garlic's ability to lower blood pressure, decrease oxidative stress, and/or prevent platelet aggregation has led to a tendency toward the assumption that garlic could play a role in preventing preeclampsia [23].

Allicin, a strong-smelling sulphide, known as the main active component in garlic. Crushing or chewing the raw garlic cloves, alliin changes to allicin, the main sulphur compound, by the action of the enzyme alliinase. Allicin has several health-promoting properties, including the ability to decrease cholesterol and blood pressure. On the other hand, the redox status of the cell buffered by glutathione (GSH). Allicin may also modify the cell's redox potential by oxidizing the glutathione pool, causing cells to enter apoptosis. Consumption of garlic supplements for 9 weeks by pregnant women at risk of preeclampsia resulted in an important rise in plasma GSH levels. Consuming garlic pills for nine weeks led to a reduction in the incidence of preeclampsia compared to women taking placebos, though the difference was not statistically significant [24, 25].

According to a recent RCT, evaluating the effects of garlic on the prevention of preeclampsia in high-risk women, overall cholesterol levels fell, but neither hypertension nor preeclampsia was reduced. In addition, minor side effects such as nausea and a foul odor have been recorded. In another study, garlic consumption linked to a lower risk of both early and late preterm birth. However, there was not any clear relationship between garlic and preventing preeclampsia and its complications. In these studies, the difference between garlic takers and placebo consumers was that those advised to take placebo [26, 27].

Besides the potential effects discussed above, garlic and its components have been shown to have antihypertensive properties *in vitro* and *in vivo*. During *in vitro* and animal experiments, garlic and its sulfur-containing components suppressed NF- κ B activation, iNOS, and COX-2 expression, resulting in

anti-inflammatory effects. Also, garlic could stimulate the production of NO and inhibit ACE activity [15]. Moreover, organic polysulfides produced by garlic constituents can be converted into hydrogen sulfide by RBCs that acts as a vasodilator; inhibiting platelet aggregation, and increasing the production of nitric oxide, as well. Intake of 4 g of garlic also boosted the action of NOS from 0.21 to 0.45 nm in platelets and nitrite levels in plasma increased from 3.9 to 7.8 μmol . Although all these results lead to the hypothesis that garlic could be effective in preeclampsia, the effect of garlic remains unclear and uncertain [15, 28, 29]. Although garlic has the potential to lower blood pressure, reduce oxidative stress, and prevent platelet aggregation, or both, or even may have a role in the prevention of preeclampsia, there is no exact recommendation for standard garlic consumption [30].

St. John's wort:

St. John's Wort (SJW), is one of the most prevalent herbal treatments for over a hundred years because of its beneficial properties. The aim of many studies was to assess the possible effects of exposure to this herb and the consequences for mother and fetus involving significant fetal abnormalities or infant adverse outcomes. SJW is well tolerated according to studies, and especially on the 10th day postpartum, SJW aided in the healing of cesarean wounds and reduced scar formation. Moreover, at the 40th day postpartum, discomfort and pruritus were reported to be greatly reduced [26].

SJW contains high concentrations of bioactive constituents that interact with the cytochrome P450 system (CYP3A4) and inhibit a membrane-bound transporter that facilitates transport across the intestinal lumen and the blood–brain barrier, making it more important. Although SJW and its components could reduce the oestrogen plasma concentration by interacting with oral contraceptives, there is no evidence of an increased risk of major abnormalities and malformations or prematurity in infants born to women who consumed SJW during pregnancy. When COCs are combined with SJW, the food-drug interaction can increase the chance of ovulation and breakthrough bleeding, raising concerns about diminished contraceptive efficacy. The pharmacokinetic evidence is controversial. However, it appears that SJW treatment is linked to a weak to moderate activation of combination oral contraceptive metabolism [31].

Coming from St John's Wort, *Hypericum perforatum* (*Hypericaceae*) has been used because of its bioactive substances, including hypericin, hyperforin, and flavonoids, in many diseases, such as major depressive disorder (MDD), which affect the neurotransmitter systems. This feature of St John's Wort makes it beneficial for depression treatment. Herbal therapies are frequently utilized by pregnant or breastfeeding women since they are thought to be safe and harmless. Large consumption of SJW causes the need for more studies around its safety, since its effects on the developing fetus as well as the nursing newborn are mostly unclear. Studies on rats indicated that chronic treatment with SJW throughout pregnancy or lactation is thought to be the cause of histological changes in the liver and kidneys [31, 32].

Observational research found no changes in significant malformations, live birth, or preterm rates among three groups of pregnant women: those who used St. John's Wort, those who took a traditional depression treatment, and healthy women who did not take any medication. According to the findings, if women use alternative anxiety treatments that are either ineffective or ineffective compared to traditional treatments, they may experience substantial maternal and child health difficulties. The findings indicated that St. John's Wort might be used to provide early clinical evidence of prenatal safety [33].

Unlike previous studies, other investigations show that though there was no convincing relationship between SJW and pregnancy consequences (e.g. head circumference, preterm birth, length and birth weight, gestational age), the incidence of malformations in the women consuming SJW was higher than in the unexposed pregnant women. This herb is frequently used in parallel with antidepressant medicines that are processed by CYP enzymes. So, potentially causing changes in their plasma concentrations is so feasible and this may raise the antidepressant medication's teratogenic potential, if such an impact exists [34].

Turmeric:

Turmeric is a ginger-like blooming plant with roots that are used in cooking. Curcuminoids, such as curcumin (diferuloylmethane), demethoxycurcumin, bisdemethoxycurcumin, and tetrahydrocurcumin,

are the most active components of turmeric. Curcumin is the natural pigment for the yellow color in turmeric. There are many studies about its possible anti-oxidant, anti-inflammatory, anti-cancer and anti-angiogenic effects on cells. *In vitro* studies illustrated a free-radical scavenging role for curcumin. Along with preventing oxidation, it also inhibited lipid peroxidation (particularly LDL) and oxidative damage to DNA (deoxyribonucleic acid). Recent research focuses on the proinflammatory cytokine reduction effect of curcumin on placental diseases, including preeclampsia and preterm birth [15, 35].

The antioxidant effects of turmeric, especially curcumin, have been proved in many studies. On the other hand, oxidative stress is one of the concerns during pregnancy due to physiological changes in pregnant women and is thought to be one of the most important contributors to teratogenesis. As maternal circulation is closely related to fetal circulation during pregnancy and the liver is the primary site of drug processing, oxidative stress in the maternal system may cause oxidative stress in the fetuses. All this can lead to consequences such as birth defects. This could be more common and possible in mothers with epilepsies who have undertaken medical treatments. Most of the time, medical administrations initiate ROS via impaired glutathione homeostasis [36].

Curcumin, as mentioned before, has the ability to suppress superoxide production, inhibit lipid peroxidation and scavenge free radicals. It was shown in studies with animal models that curcumin was as effective as phenylbutazone in treating acute inflammation. Its significant antioxidant properties, suppression of cell signaling pathways, broad effects on cellular enzymes, and inhibition of a variety of inflammatory chemicals could all be considered forerunners to these findings. Curcumin has immunomodulatory effects as well. This component of turmeric acts as primarily immunosuppressive. Moreover, results of studies indicated that turmeric enhanced wound healing, one of the reasons it is traditionally used in postpartum recovery [37].

Furthermore, turmeric has a powerful inhibitory effect on COX-2, leukotrienes, prostaglandins, and other inflammatory mediators such as TNF- α , and NF- κ B. According to an investigation, daily consumption of 1 gram per day, as curcumin supplementation, over 8 weeks considerably diminished serum levels of proinflammatory cytokines in patients suffering from metabolic syndrome. It also leads to decreases in TNF- α , IL-6, and TGF- β plasma concentrations [15].

Furthermore, in a 12-week study on albino mice, oral intake of 0.5 percent turmeric (0.015 percent curcumin) resulted in no considerable differences in the number of dead and live embryos; pregnancy and implantation rates were normal; and body weight did not differ notably between the two groups. In this study, it was also illustrated that curcumin during pregnancy is a safe, nonmutagenic and nongenotoxic agent [38].

Curcumin repressed glucose in the liver and reduced blood glucose levels, reversed insulin resistance in fat cell cultures, increased glucose absorption into skeletal muscle, and stimulated pancreatic beta-cell function, according to *in vitro* and *in vivo* animal experiments. All these mechanisms end up with better blood glucose level controls. Unfortunately, there is no clear evidence that indicates *curcumin* metabolites are just as potent as *curcumin* itself [15, 36].

Chamomile:

Chamomile is one of the well-known ancient therapeutic herbs that belongs to the *Asteraceae/Compositae* family and is characterized by two common varieties: *Roman Chamomile (Chamaemelum Nobile)* and *German Chamomile (Chamomilla recutita)*. The flowers of this herb consist of terpenoids and flavonoids, providing its remedial qualities. Aromatherapy of chamomile essential oil is vastly consumed by pregnant women in order to decrease anxiety without changing the delivery outcomes during the gestational period, as reduction of childbirth anxiety via chamomile essential oil is acclaimed in studies [39].

Improving the symptoms of pregnancy is one of the most important reasons that leads women to try herbal medicines. Eugenol (extracting from holy basil) and α -bisabolol (from chamomile; at a high concentration of 80 μ M) are the active phytochemicals that are involved in calmness and reducing stress in consumers [40, 41]. Chamomile has anti-stress characteristics that encourage pregnant individuals (particularly in unplanned pregnancy situations) to consume this herb. Though chamomile has positive effects, bisabolol enhanced ROS creation and declined cell activity, which most likely results in cell

death. However, low to moderate levels of bisabolol (0.01- 20 μ M) did not lead to any teratogenicity effect, unless high concentrations (40 and 80 μ M) occurred [41].

After consistent consumption of chamomile in pregnant women, different gestational complications have been shown in studies. Steady users of chamomile were found to have an upper risk of low birth weight than non-users in studies. Moreover, regular and frequent use of chamomile also results in a shorter gestational age at birth and a shorter newborn. The etiology of preterm birth and shorter gestational age is not clear, and needs more studies. However, studies have pointed out regular chamomile consumption as a risk factor for these conditions. Though there are still studies that indicate no higher risk of lower birth weight in pregnant chamomile users, chamomile consumption should be cautiously [42].

In general, there are still concerns about chamomile intake during pregnancy. Chamomile has been linked to severe anaphylaxis, a life-threatening allergic reaction that develops quickly and can be lethal. Likewise, pregnant women with coagulation disorders throughout pregnancy should avoid this herb since it has been categorized as a coumarin-derivative plant. Thus, drug-food interaction of this herb should be considered [42].

Peppermint:

Another debilitating condition during pregnancy which affects many pregnant women is nausea and vomiting of pregnancy (PNV). Reducing the time it takes to prepare food, consuming more of the appealing foods, allowing food to digest before sleeping, eating in a comfortable environment, drinking 30 minutes before or after meals, but not during them, drinking a cup of honeyed herbal tea is among the nutritional related guidelines and recommendations for pregnant women to reduce this complication and improve the mother's quality of life [43].

Besides these available recommendations, there are studies suggesting aromatherapy of peppermint to relieve nausea or vomiting throughout pregnancy's first trimester and also during labor. In these studies, mint has been used to lessen morning sickness during pregnancy. As studies in rats indicated that peppermint essential oil's oral intake reversibly decreases gastric acid secretion, thus, recommending it to patients with gastrointestinal problems could be beneficial [44].

Heartburn, Gastroesophageal Reflux Disease (GERD), and Acid Reflux Disease are all terms identifying acid reflux disease, which could be triggered by pregnancy, heavy meals, excessive weight, sleep deprivation, and sleeping insufficiently. In pregnancy, GERD is known as heartburn and seen in 45-80% of pregnant women, and most of it happens in the first trimester. The progesterone and estrogen hormones that lead to a relaxation of the muscles (e.g. the gastrointestinal tract muscles), increase the frequency of bowel movements. Along with muscles, the lower esophageal sphincter will be induced, as well, resulting in acid reflux. All forms of peppermint intake (e.g. tea, digestive tablets, candy or essential oil) have carminative properties [45].

However, side effects such as heartburn may occur in cases given essential oil of peppermint. To decrease this complication, it is recommended to consume peppermint after a meal to diminish gas and reduce the time of food staying in the stomach, and help with digestion. Furthermore, peppermint performs the role of an anesthetic agent to the stomach wall and comforts nausea and vomiting. Studies illustrated utilizing peppermint tea (1 cup of boiling water with 2 dried peppermint spoon leaves for 10 minutes with tea) in between meals for 1 month improved GERD symptoms [45].

Pepper:

Known as one of the world's most important spices, pepper has a special value due to its influence on the world's spice trade. There are different types of pepper coming from a plant with different processes, including red, black, green, and white. The mature seed is red, the immature seed is green. To get black, it should be dried and the skin removed seeds are white [46].

Black pepper contains alkaloids, piperine, wisanine, and dipiperamide. However, the main active constituent of black pepper is piperine (accounts for 5 - 9%), which is mostly used as a traditional medicine. In *in vitro* studies, piperine has been demonstrated to protect against oxidative damage by blocking or quelling free radicals and reactive oxygen species (ROSs) [15].

It has also been evidenced via studies that black pepper (piperine as the main ingredient) reduces lipid peroxidation and improves cellular antioxidant capacity in a variety of oxidative stress situations. Moreover, black pepper may speed up the digestive progression by enhancing gastric acid and bile acid secretion, increasing digestive enzyme activity, and decreasing food transfer time. When piperine is ingested through food, it has been found to increase the activities of pancreatic amylase, lipase, and chymotrypsin [15].

Paprika, another type of pepper, is widely used as a natural food color and flavor. It is harvested as a vegetable as well as a source of spice, and at the same time, it contains numerous essential vitamins and other nutrients. Because of the presence of capsaicinoids (0.2 – 2%) in the fruits of spicy varieties, paprika has become a valuable raw material in the pharmaceutical business [47].

Capsaicin, an alkaloid substance, constitutes between 50 to 70 percent of the total capsaicinoids, and is followed by dihydrocapsaicin (found 20–25% in red pepper). These nonpungent compounds are responsible for their antioxidant roles, which have been shown to alleviate oxidative stress features in numerous organs or tissues. Capsaicin has been shown in animal studies to lower vascular permeability and proinflammatory cytokine production by preventing neutrophil (inflammatory cells) migration toward the inflammatory focus; reduce obesity-induced inflammation by inhibiting macrophages from releasing proinflammatory mediators *in vitro*; and regulate messenger molecules generated by obese mice fat cells [15].

Other studies have suggested that red pepper may influence beta-cell insulin secretion and/or peripheral insulin resistance, as well as diminish hepatic glucose synthesis and develop glycogen storage. These findings were confirmed in clinical trials where consumption of 5 grams or more of chili pepper in humans was related to a reduction in serum glucose level and preservation of healthy insulin levels. Although red pepper improves fat oxidation and thermogenesis, it affects heart rate and blood pressure; thus, long term intake of capsaicin may also be restricted [15].

Fennel:

Though fennel is believed to be safe for breastfeeding, it may be dangerous during pregnancy. Fennel consumption on a regular basis may increase the risk of small gestational age of neonatal at birth. On the other hand, being used as an estrogenic therapy for a thousand years, fennel has been suggested to incite menstruation, improve female climacteric symptoms, assist delivery and increase lactation [42].

Fennel has the ability to impede isolated uterine contractions stimulated by PGE2 and oxytocin. As mentioned before, anethole, dianethole, and photoanethole are the key components of the fennel that show estrogen-like features. Hence, there are concerns about fennel's potential negative impact on fetal development in pregnant women consuming it during gestational periods [48].

In addition, other compounds isolated from fennel have been proved to have interactions with cytochrome P4503A4, which is closely related to medicine metabolism; thus, there could be a possible food-drug interaction. It was also shown in studies that fennel tea consumption has a relationship with highlighted the importance of fennel tea as an inevitable reason for premature thelarche and breast development in prepubertal girls [49].

Fennel intake as extract at concentrations ranging from 100 mg per kg to 200 mg per kg can enhance estrogen levels; more than these concentrations cause increases in progesterone levels and prolactin serum levels, as well. Moreover, fennel extracts have the ability to diminish pre-menstrual syndrome (PMS) severity, and studies have recommended consumption of this extract in order to relieve PMS signs and symptoms [50].

2. Conclusion

While most healthcare professionals indicated concerns about the patient's self-initiated complementary safety and herbal product intake in pregnancy, the suggestions still remain controversial. As herbal products have different effects, most of which are unclear, it would be better to be more cautious while consuming them, especially in pregnancy and in dosages greater than common routine doses.

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