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**Herbal dietary habits on liver enzymes and oxidative stress**

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## Abstract

Herbal plants are a significant source of several nutrients that are essential for human and animal diets and are used to prevent or treat ailments. These elements are essential nutrients for their survival and must be obtained through diet because the body cannot generate them. The Saudi market is brimming with numerous medicinal plants that citizens use as "traditional medicine," many of which are imported from Asia and Africa, while the remainder is harvested locally. They are also used in cooking, cosmetics, and up to 80% of the world's population relies on plant-derived medications for medical purposes. This review provides information on Saudi individuals' consumption of herbs and their composition to assess the toxicity of the essential oils of myrrh, marjoram, senna, and asafoetida plants. A systematic search was performed in PubMed, Google Scholar, Embase, the Cochrane library, and Web of Science, for studies that investigated Herbal dietary habits on liver enzymes and oxidative stress. In this review we found that the most common side effects of the long term usage of the herbal plants are eyes or skin irritation, stomach discomfort, cramps, and diarrhea. In some cases, there is liver damage. Furthermore, the findings of this review serve as a foundation for future studies of herbal plants in Saudi Arabia, as well as characterize patterns of practise among Saudi individuals.

**Keywords:** Myrrh, Marjoram, Senna, Asafoetida, herbal plants, liver enzymes, Toxicity.



## المخلص

تعتبر النباتات العشبية مصدرًا مهمًا للعديد من العناصر الغذائية الضرورية للوجبات الغذائية للإنسان والحيوان وتستخدم للوقاية من الأمراض أو علاجها. هذه العناصر هي العناصر الغذائية الأساسية لبقائهم على قيد الحياة ويجب الحصول عليها من خلال النظام الغذائي لأن الجسم لا يستطيع إنتاجها. يزخر السوق السعودي بالعديد من النباتات الطبية التي يستخدمها المواطنون كـ "طب تقليدي"، وكثير منها مستورد من آسيا وأفريقيا، فيما يتم حصاد الباقي محليًا. كما تُستخدم أيضًا في الطبخ ومستحضرات التجميل، ويعتمد ما يصل إلى 80٪ من سكان العالم على الأدوية المشتقة من النباتات للأغراض الطبية. تقدم هذه المراجعة معلومات عن استهلاك الأفراد السعوديين للأعشاب وتكوينها لتقييم سمية الزيوت الأساسية لنباتات المر، والمرdqوش، والسنا، والحلافة. تم إجراء بحث منهجي في PubMed و Google Scholar و Embase ومكتبة Cochrane و Web of Science للدراسات التي بحثت في العادات الغذائية العشبية على إنزيمات الكبد والإجهاد التأكسدي. في هذا الاستعراض وجدنا أن الآثار الجانبية الأكثر شيوعًا للاستخدام طويل الأمد للنباتات العشبية هي تهيج العين أو الجلد، وعدم الراحة في المعدة، والتشنجات، والإسهال. وفي بعض الحالات يكون هناك تلف في الكبد. علاوة على ذلك، تعمل نتائج هذه المراجعة كأساس للدراسات المستقبلية للنباتات العشبية في المملكة العربية السعودية، بالإضافة إلى تمييز أنماط الممارسة بين الأفراد السعوديين.

**الكلمات المفتاحية:** المر، البردقوش، السنا، الحلتيت، النباتات العشبية، إنزيمات الكبد، السمية.



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مجلة الدراسات الجامعية للبحوث الشاملة

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## Introduction

The liver is a complicated organ that plays a key role in the metabolism of important macronutrients including carbohydrates, proteins, and lipids. The liver also releases enzymes in a certain pattern, just like every other organ in the body. Indicators of hepatic metabolic and excretory capacity include enzymes such alanin aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT), which are mostly secreted by the liver and considered the key biomarkers of liver dysfunction in the general population (**Lorzadeh et al., 2021**).

Numerous chronic disorders are thought to be related to high levels of ALT, AST, ALP, and GGT in the blood. For instance, an increase in serum ALT and GGT may be accompanied by a decline in glucose tolerance, which may result in diabetes mellitus. Additionally, GGT has been linked to the metabolic syndrome. A common disorder is fatty liver, which is further broken down into alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). A high AST/ALT ratio in AFLD is more common in patients with advanced disease (**Liu et al., 2020**).

The term "oxidative stress" a preponderance of oxidants over antioxidants, this can cause molecular damage and/or a breakdown in redox signalling and regulation. Degradation of proteins, lipids, and DNA can occur in cells as a result of oxidative stress, which is defined as high amounts of reactive oxygen species (ROS) and an unbalanced ratio of antioxidants to oxidants. Reactive oxygen species (ROS)



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play a role in the liver fibrogenic response and are involved in necrosis, apoptosis, and ischemia/regeneration. As a result of these alterations, gene expression is changed and liver damage progresses (**Sies, 2015**).

Herbs play an essential role in politics, romance, religion, and health, and they are still utilised by millions of people around the world, particularly as medicine since they contain more than 50 components that are a major component of enzymes and proteins. And because optimal nutrient intake may lower health risk, their use is expanding globally due to their modest side effects when used moderately (**Tokaloğlu Ş., 2012**).

The majority of the herbs is naturally grown in numerous parts of the world and has been used since ancient times. They are also used in cooking, cosmetics, and up to 80% of the world's population relies on plant-derived medications for medical purposes. Green tea is also a fantastic illustration of how herbs have been used for ages in China and Japan and are being used now. However, for safety reasons, it is recommended that different contaminants be assessed before supplying such herbs to the end user (consumer) (**Jaksevicius A., et al., 2017**).



Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

The Saudi market is brimming with numerous medicinal plants that citizens use as "traditional medicine," many of which are imported from Asia and Africa, while the remainder is harvested locally. Studies on the elemental composition of these plants obtained from the Saudi market are rare, and studies on herbal preference among citizens and their knowledge base have not before been conducted. As a result, the findings of this study serve as a foundation for future studies of herbal plants in Saudi Arabia, as well as characterise patterns of practise among Saudi individuals (**Almahasheer, H. 2020**).

### **Significance of study**

Natural remedies are being used more frequently to cure a variety of human illnesses. For such natural items to be used safely and properly, toxicity evaluation is crucial. Even while a natural product may not always be hazardous, a higher dose might nonetheless cause toxicity. They may occasionally be toxic to a specific organ, leading to tissue damage or metabolic malfunction. So, from the assessment of toxicity, we may learn a lot about the efficacy and safety of using natural products. The purpose of this study was to assess the toxicity of the essential oils of myrrh, marjoram, senna, and asafoetida. Their use is expanding daily in many nations. Although numerous biological activities have been documented, toxicity and safe assessment have not yet undergone in-depth research. We sought to determine the toxicity and impact on the liver enzymes in this investigation.



Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

## Objectives

1. Determine the effect of Senna on liver function and oxidative stress.
2. Determine the Effect of Asafoetida on liver function and oxidative stress.
3. Determine the Effect of Marjoram on liver function and oxidative stress.
4. Determine the Effect of myrrh on liver function and oxidative stress.

## Search strategy

A systematic search was performed through 2022, the databases of PubMed, Web of Science, Scopus, and Google Scholar were searched using both terms from the Medical Subject Heading and terms from terms other than the Medical Subject Heading for studies that investigated Herbal dietary habits on liver enzymes and oxidative stress The following keywords were employed: (Diet, herbal, Senna, Asafoetida, Marjoram, or myrrh is some examples.) And (liver, liver enzyme, lactate dehydrogenase OR L-Lactate or Oxidative stress).



## Literature review

### 1. Senna plant

Senna is a member of the Fabaceae family (Leguminosae). One of the larger genera, it has between 300 and 350 species and was once categorized under Cassia. Many Senna species are utilized in both traditional and contemporary medicine, as well as ornamentals, famine foods, and shade plants (Sobeh et al., 2017).

*Senna alexandrina*, is a tiny, perennial plant that grows in Sudan and Egypt near the River Nile in North Africa. It is a member of the Caesalpiniaceae family. Apigenin-6,8-di-C-glycoside, aloe emodin, kaempferol, isorhamnetin-3-O-beta-gentiobioside, D-3-O-methylinositol, and emodin-8-O-beta-D-glucopyranoside are the seven pharmacologically active substances found in its leaves. Traditional uses of senna alexandrina include its antioxidant and anti-inflammatory qualities, but nothing is known about how it might protect against cadmium, a common environmental toxin that causes hepatotoxicity (Wang et al., 2019).

*Senna singueana Delile*, also known as wild Cassia or Senna singueana, it is extensively distributed in the tropics and is made up of shrubs and trees. This genus has been associated with flavonoids, anthraquinones, stilbenes, terpenes, alkaloids, and proanthocyanidins, among other groups of secondary metabolites. Additionally, it is a traditional African medicinal herb (Sobeh et al., 2017).





Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

The plant is traditionally used to cure a variety of conditions throughout Africa, including fever, skin cancer, and malaria as well as diabetes, stomachaches, leprosy, rheumatism, microbiological and sexually transmitted diseases, and inflammation. A plant root decoction is used to cure constipation in the rural areas of southern Sudan. Northern Ethiopian species' leaves and bark extracts have been demonstrated to scavenge free radicals and prevent erythrocyte hemolysis (**Sobeh et al., 2017**).

The wide range of phytoconstituents found in the leaves, stem, and seeds of the Senna plant contribute to these positive benefits. More than 350 components, as well as 40 secondary metabolites, were isolated from *Senna spectabilis* (DC.) These phytochemicals mostly consisted of piperidine alkaloids and classes of pentacyclic triterpenes with beneficial effects on health (**Nayan SI, et al., 2021**).

Senna plants have been examined for their potential pharmacological effects, which include anti-infectious, antioxidant, anti-cryptococcus, antitumor, anti-mutagenic, anti-plasmodial, anti-inflammatory, anti-cancer, antidiabetic, wound-healing, and antihelminthic properties. Due to the presence of phenols and flavonoids, Senna plants have been demonstrated in some studies to have anti-diabetic properties (**Alshehri et al., 2022**).

Despite the great range of medical applications that many herbal items may have, exposure to some of these botanicals may be hazardous to both people and animals. In a similar vein, some Senna species, particularly their seeds, are



reportedly poisonous in various ways despite having a wide range of purported health benefits (**Gebrezgi et al., 2020**).

Supplementing rats receiving a high-fat diet with *S. alexandrina* leaf powder stopped the rise in cholesterol and triglyceride levels. Moreover, *S. alexandrina*. Additionally, nitric oxide generation and lipid peroxidation were decreased in these rats by *S. alexandrina* leaves prevents oxidative stress from occurring. In high-fat diet-fed rats, *alexandrina* leaf supplementation is controlled by increasing antioxidant enzyme activity, which is followed by the restoration of related gene expressions, the ability of *alexandrina* leaf supplementation to reduce fibrosis and inflammation in fatty livers raises the possibility that it can be used to treat non-alcoholic steatohepatitis. Therefore, this natural leaf extract has the potential to treat liver dysfunction caused by obesity (**Nayan et al., 2021**).

By monitoring the blood levels of hepatic transaminase enzymes like ALT, AST, and ALP, the health of the liver can be evaluated. These enzymes' elevated blood levels are a sign of liver damage or the beginning of hepatic degeneration. An essential factor in this process is early oxidative stress in tissues. According to Nayan et al., study, the HF group had higher levels of these liver marker enzymes than the control group did. Previous scientific researchers have also backed this conclusion. However, liver function marker enzyme activity was decreased by supplementing with *S. alexandrina* leaves (**Yuan Y., et al., 2019**).



Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

## Toxicity of Senna plant

Senna's potential for toxicity is often underestimated, and poisoning cases are rarely reported. It is quite difficult to ascribe this seemingly benign drug to the clinical presentation, which mimics severe liver failure. There is a rare instance of a senior citizen who developed a hepatoencephalopathic syndrome after ingesting *Senna occidentalis* and explains the multisystem pathophysiology of this fast progressing illness (**Ish et al., 2019**).

Rapidly progressing hepatomyoencephalopathic illness *Senna occidentalis* has a significant fatality rate. This plant has poison in every component. Due to ignorance and the lack of prescription information, toxicity may go unnoticed. When individuals present with vomiting and diarrhea and then rapidly progress to liver failure, it would be good to have a high index of suspicion (**Chhapola, et al., 2018**).

*Senna alata* was a part of a two-year intensive monitoring programme in Thailand for negative effects. Five reports of adverse reactions for human use of *Senna alata* were found in the nation's national vigilance database of herbal products between 2000 and 2008, including a diminished therapeutic effect over time, eyelid swelling, nausea, vomiting, headache, and skin rash (the plant part and type of administration were not specified) (**Saokaew et al., 2011**).



Rats given dried, crushed *Senna alata* leaves combined with their food for 2 or 4 weeks manifested some liver, kidney, and intestinal damage (lesions). Rats fed a 100 mg alcohol extract of *Senna alata* in their water displayed liver lesions (**Ish et al., 2019**).

## 2. *Asafoetida*

The Umbelliferae family includes the monoecious, herbaceous, perennial plant known as *Ferula asafoetida*. The Latin word *asafoetida*, which has two syllables, meaning "stinky gum." (**Mala et al. 2018**)

*F. asafoetida*'s oleo gum resin is made from the exudates of the plant's roots and rhizomes include resin (40–65%), *Asafoetida* volatile oil (5–20%), and gum (20to25 percent). *Asafoetida* contains a lot of sesquiterpenes, including *Asafoetidnol A* and *Asafoetidnol B*. Oleo gum resin contains galbanic acid and ferulic acid. It also contains carbohydrates (67.2%), moisture (16%), protein (4%) and fat (1.1%), as well as minerals (7.0%) and fibres (4.1%). *Asafoetida* gum ranges in colour from yellowish-white to reddish brown and has an acrid, bitter, and alliaceous flavour (**Mahboubi, 2022**).



Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

Since ancient times, asafoetida has been used as a spice in Indian cuisine and medicinal. It has also been used in folk phytomedicine since antiquity to treat a variety of neurological, gastrointestinal, respiratory, endocrine, and reproductive disorders. These include epilepsy, paralysis, hysterias, depression, and intestinal parasites (premature labour, unusually painful, difficult and excessive menstruation, leucorrhoea, and infertility) (**Sharma et al., 2018**).

Studies have been done on the following: the treatment of human cancer, periodontal disease, and gut problems; their influence on digestive enzyme activities and gut microbiota; and as food additives due to their distinctive odour. The therapeutic actions of this genus were highly accepted. To the best of our knowledge, this genus has only been studied previously in relation to animals, and there are few records of it being used in other contexts, such as aquaculture (**Hashemi et al. 2019**)

A mixture of fresh garlic, curcumin, ellagic acid, butylated hydroxytoluene, and butylated hydroxyanisole, combined with the methanol-insoluble fraction of dried resin, has been shown to have antihepatotoxic activity against aflatoxin B1-induced hepatotoxicity when given by gastric intubation to ducklings at a dose of 10 mg/animal. Oleoresin has been proven to inhibit hepatic oxidase when given to rats at a level of 250 mg%. (**Mahendra & Bisht, 2012**)

Since the liver is the organ in charge of detoxifying medications and chemicals, all harmful compounds are first directed at it. Studies have shown that CCl<sub>4</sub> plays a part in causing damage to the liver tissue that results in lipid peroxidation and, ultimately, liver fibrosis. Hepatocellular injury, multilobular



Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

necrosis, and a mononuclear cell infiltrate are among the histological signs of severe CCl<sub>4</sub>-induced liver damage. A study of Sharma et al., showed that the extract of oleogum resin may successfully guard against the loss of antioxidants brought on by the injection of CCl<sub>4</sub> and prevent the production of compounds that cause liver damage. Numerous studies have been published that support the idea that flavonoids act as antioxidants and may guard against oxidative stress brought on by environmental factors. The increased reactivity of the hydroxyl substituents, which contributes to their capacity for radical scavenging, has been linked to flavones' antioxidant potential (Sharma et al., 2018).

### **Toxicity of Asafetida**

Different nations utilise asafetida not only as a culinary spice but also as a traditional medicine to treat a number of ailments. Although there are no experimental evidence regarding the toxicity effects of asafetida, it was stressed in Iranian traditional that use of higher dosages of asafetida might result in lip swelling, digestive complaints such gas and diarrhoea, pain, and headache (Emami A., et al., 2010)

Any substance or medication with an oral LD<sub>50</sub> estimate larger than 1,000 mg/kg, according to Clarke and Clarke could be regarded as having low toxicity. This demonstrates that asafetida was determined to be risk-free for mortalities up to 1,000 mg/kg body weight (Appidi JR, et al., 2009).



Acute toxicity of asafetida caused a significant increase in AST and LDH level in treated animals as compared to control group, LDH and AST are considered to be sensitive indicators of hepatocellular damage and within limit can provide a quantitative evaluation of the degree of damage to the liver. A study of Bagheri, et al., showed that asafetida did not have any acute toxicity, but the chronic consumption of this oleo-gum-resin caused reverse effects on liver and blood parameters (Bagheri SM., et al., 2015).

### 3. Marjoram

*Origanum majorana* is a plant with excellent antioxidant and anticancer qualities that is used as a spice and a crude medication all over the world. In Egypt, the entire marjoram plant is gathered and used. The plant grows to a height of about ten inches and produces tiny white or occasionally pink blooms. From the plant's leaves and flowering tips, sweet marjoram oil is extracted (Yousefi, M., et al., 2021).

Flavonoids, tannins, sterols, triterpenes, and volatile oils were among the phytochemical components of *Origanum majorana* that had previously been isolated and identified. Additionally, the chemical make-up of the extract from *Origanum majorana* leaves was determined. There were discovered about 26 volatile components. Terpinen-4-ol, -terpinene, trans-sabinene hydrate, linalool,



Journal of University Studies for inclusive Research (USRIJ)  
مجلة الدراسات الجامعية للبحوث الشاملة

ISSN: 2707-7675

trans-sabinene hydrate acetate, thujanol, terpinolene, and thymol were discovered to be the main ingredients (**Afifi et al., 2014**).

This plant has shown useful in conventional and herbal treatment in addition to being used as a garnish and flavouring. Traditional uses include alleviating migraine headaches, easing tense muscles and reducing spasms, calming and fostering peaceful sleep, soothing the heart, lowering high blood pressure, assisting breathing, and cleaning. Other researchers have further demonstrated marjoram's potential anti-oxidant capacity and its preventive action against liver damage (**Ghaeni Pasavei et al., 2020**).

It is grown for its flavorful leaves, which are also used for other culinary uses. It tastes well in salads as well. Numerous folkloric medical claims relating to marjoram have been supported by various experimental models. In Egypt and Arabia, it is a popular at-home treatment for stomach problems, flatulence, rheumatic pain, neurological disorders, cardiovascular diseases, epilepsy, and sore throats. Marjoram has a high polyphenolic content, which contributes to its excellent antioxidant potential. In addition to stimulating the digestive system, marjoram has hypoglycemic, diuretic, and antibacterial properties (**Moubarz et al., 2022**).

Numerous ingestible or therapeutic plants, including green tea, curcuma longa, nigella sativa, and marjoram oil, have been shown to be able to shield the liver from oxidative damage due to their anti-oxidant properties. *Origanum majorana* can shield the liver from NFLD brought on by oxidative stress. The anti-oxidant substances flavonoids, anthocyanins, tannin derivatives, and rosmarinic acid





are responsible for this protective action. As a result, incorporating these medicinal herbs into a treatment plan may lessen the negative effects of chemical agents (Ghaeni Pasavei et al., 2020).

*O. majorana* aerial component extracts in water, essential oil, and ethyl acetate have notable antioxidant activity. Other sweet marjoram extracts, such as ethanolic, n-hexane, and hydroalcoholic extracts, have also been said to possess antioxidant effects. Antioxidant action is caused by phenolic molecules such hydroxycinnamic acid and flavonoids, ursolic acid, carnosic acid, carnosol, rosmarinic acid, and caffeic acid (Bina & Rahimi, 2016).

### **Toxicity of *O. majorana***

Long-term usage or application of fresh marjoram to the skin or eyes could be dangerous. There is some evidence to suggest that long-term usage of marjoram may result in cancer. Applying fresh marjoram could irritate eyes or skin. Additionally, *O. majorana* extract in mice has shown to have a wide margin of safety in acute toxicity tests. During pregnancy, pregnant women should be cautious of sweet marjoram's emmenagogue effects. Pregnant and lactating women must not use its essential oil (Bina & Rahimi, 2016).

It is mostly used in herbalism to treat various gastrointestinal issues and to promote digestion. Recent studies revealed that this plant was secreting more acid and pepsin. In the digestive tract, sweet marjoram also exhibited antiulcer action and mucus-protecting properties. The restoration of hormonal balance and lowering of DHEA-S by this plant can be related to *O. majorana*'s ethnomedical usage on



vaginitis and polycystic ovarian illness. It has been demonstrated that *O. majorana* has antiplatelet and cardioprotective properties, which may be connected to its reduction of nitric oxide and lipid peroxidation production in heart tissues. **(Bina & Rahimi, 2016).**

#### 4. Myrrh

The oleoresin exudates produced by the bark of *Commiphora* trees, especially *Commiphora molmol* (Burseraceae), are known as myrrh (or its synonym *Commiphora Myrrha*). In Saudi Arabia and the Arab world, the aromatic yellowish-brown oleoresin has a long history in folk and traditional medicine. When applied topically or used as mouthwash, the water extract of the oleoresin was traditionally used to cure wounds and ulcers **(Younis & Mohamed, 2021).**

Furthermore, the topical use of excaudate extract aids in the reduction of headaches, muscle pain, and cramps. In Chinese traditional medicine, myrrh was used with frankincense to promote blood circulation and flush out blood stasis internally. In addition to being used in conjunction with curcuma, garlic, and iron to prevent and treat hypertension, myrrh is also taken internally to treat anemia. Myrrh was used in Ayurveda to treat obesity, gynaecological, coronary artery disease, and inflammatory illnesses **(Younis & Mohamed, 2021).**

Myrrh extract and fractions (obtained through hydrodistillation) has been the subject of numerous published biological researches. According to some reports, myrrh can be used to treat diabetes, furunculosis, respiratory catarrh, schistosoma,



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ISSN: 2707-7675

and ulcers. Additionally, it was discovered that myrrh enhanced the healing of wounds by promoting the permeability of medicine from the epidermis to the dermal capillaries (**Lamichhane et al., 2019**).

One of the earliest known drugs for the treatment of inflammatory illnesses is myrrh. Its various phytochemical elements have been proven in published studies to have dose-dependent anti-inflammatory, analgesic, cytotoxic, anti-septic, antibacterial, and antiviral activities. Commiphora supports sustained white blood cell proliferation and activation during healing, which means that during the efficient healing process, myrrh triggers late steps in both the proliferation and differentiation pathways for white blood cells. Commiphora reduces inflammation and controls inflammatory mediators through a variety of effective methods, increases white blood cell counts without risk. (**Abukhader & AL TAWAHA, 2021**).

A study results of Lamichhane R, et al, showed that the lower doses of Myrrh Essential Oil are safe as they had no skin nodule/inflammation and physiological damage to the organs but The higher doses of (40, and 80 ) were toxic causing damage to some organs (liver, kidney, and spleen) (**Lamichhane R, et al., 2019**).

## Conclusion

Natural remedies are increasingly being used to cure a variety of human illnesses. For such natural items to be used safely and properly, toxicity evaluation is crucial.



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**ISSN: 2707-7675**

Even while a natural product may not always be hazardous, a higher dose might nonetheless cause toxicity. They may occasionally be toxic to a specific organ, leading to tissue damage or metabolic malfunction. Therefore, through the toxicity evaluation, we may learn a lot that is helpful for ensuring the safety and effectiveness of natural goods.

The amount of nutrients present varied depending on the type of plant examined; the majority of the herbs examined fell within the Recommended Dietary Allowance (RDA) range. However, those who choose a high number of cups per day or spoons each cup may run the risk of bioaccumulation. In this review we found that the most common side effects of the long term usage of the herbal plants are eyes or skin irritation, stomach discomfort, cramps, and diarrhea. In some cases, there are liver damage.

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