Proceedings of the Pakistan Academy of Sciences:
B. Life and Environmental Sciences 56 (3): 1–9 (Special Issue, 2019)

ISSN: 2518-4261 (print), ISSN 2518-427X (online)

Pakistan Academy of Sciences

Review Article

Therapeutic and Adverse Effects of Commonly Used Medicinal Plants: Standardization and Quality Assurance

Rizwan Faisal[1], Laiyla Shinwari[2], Iram Aziz[3], and Ali Talha Khalil[4]

[1]Rehman Medical College, Peshawar
[2]Goverment Maternity Hospital, Peshawar
[3]Cantt Military Hospital, Rawalpindi
[4]Qarshi University, Lahore

Abstract: The use of medicinal plants has witnessed an upsurge because of a general perception of being economical, effective and safe relative to allopathic medications. However, converging evidence suggests unwanted allergic reactions of herbal preparations and also toxic fatal reactions in the body signifying need for the extensive toxicity assessments. Moreover, some adverse reactions can stem from the contamination of herbal drugs which is attributed to the lack of standardization and quality control of herbal drugs. Contamination of metals, microorganisms and false identification can also end up in causing toxicity and allergic reactions which demand the dire need for pharmaco-vigilance to promote safe use of herbal preparations. In this paper, we have presented a review of literature on the toxicity profiles of most commonly used medicinal plants and presented valuable recommendations to allow safe use of the herbal medicines.

Keywords: Medicinal plants, Allopathic, Allergic Reaction, Herbal Medicines, Toxicity Profiles.

1. INTRODUCTION

Plants play an integral role in the environment and have a close association with the human civilization. Plants are used for food, clothing, shelters flavors, and fragrances and also taken in a form of medicines. Herbs or herbal preparations represents first generation of therapeutic medicines which were used to cure human ailments since time immemorial [1]. Herbs have been an integral part of traditional medicine and their use is documented from at least 5000 years [2]. Folkloric medicines are either complementary or a main source of medical treatment for about 75%–80% of the world population and used mostly in under developed and developing regions [3]. In some countries these traditional practices have been integrated through regulations into mainstream health systems. The herbal industries across the world like Traditional Chinese Medicines, Ayurvedic Medicines, Greek Medicines and Greeco-Islamic Medicines are continuously expanding [4]. In spite of their medicinal uses, several plant species contains phytochemical which are poisonous; however, they are still used for therapeutic purposes in traditional or folkloric medicines. Mostly the consumers, in general have a strict narrative about the herbal medicines (HM) for being a safer option with no side effects as being made entirely of natural ingredients.

The assumption that 'natural' can be equated with 'safe' is certainly an important factor but misleading [5]. A number of plants can be poisonous and may cause toxicity [6]. These toxicity issues remained unnoticed for thousands of years, however, with the growing scientific literature has revealed toxicity of certain herbs or their preparations manifested in different ways such as hepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity etc. The advantages of the herbal treatment are considerable, however, their unregulated use can have severe consequences. These herbal medicines usually contains potent

Received: Feburary 2019; Accepted: September 2019
* Corresponding Author: Rizwan Faisal; rizwan.faisal@rmi.edu.pk

and bioactive extracts of herbs containing complex phytochemistry and pharmacologically active ingredients causing varying degree of side effects [6]. Secondary metabolites of plants are not benign as these has evolved as a part of chemical defense mechanism intended to poison, repel, stun, or kill other species. Many of the herbal preparations have reported to cause hepatitis, but identification of particular component causing the disease is difficult to identify [7]. Medicinal plants have a broad action on physiology of the body which sometimes can be adverse [8]. Thus, the narrative of plant extracts being safe is misleading and signifies the need of intensive research on the safety and interaction aspects of plant based medicines.

Therefore, it is imperative to conduct the ethno-toxicological assessment of the medicinal plants, herbal medicines or their preparations in order to identify potential and possible side effects, optimize dosage, identify contamination and separate poisonous plants. The toxicity assessments are directed towards separating medicinally valuable plants from poisonous plants and develop such combinations that are effective and possess no side effects or toxicity. Furthermore, standardization and quality control is important to control the potential contamination and prepare product of highest quality and standard.

The aim of this article is to provide an overview and critical evaluation of evidence from systematic reviews (SRs) and literature of the adverse effects (AEs) associated with the use of herbal medicines [9]. It is important to remember that it does not attempt to identify or define all AEs (Adverse Effects) of HM products: in many cases, probable AEs have been implicated but were not documented in a SR. Electronic literature searches were conducted in February 2019 to identify adverse effects of HMs used in any type of clinical condition. The following electronic databases were used: Google scholar, Cochrane and Pak Medi Net. In addition, the problems associated with the standardization and quality assurance of herbal medicine manufacturing are discussed.

1.1 Ginger Rhizome (*Zingiber officinale)*

Ginger rhizomes *(Zingiber officinale*), is a well-established medicinal plant in the folkloric scriptures and used for the treatment of infectious diseases, indigestion, arthritis, rheumatism, fever, vomiting, hypertension etc. Ginger is used as an antiemetic by 80% of pregnant women to treat nausea and vomiting in the early stages of pregnancy. Mostly studies revealed that the powdered ginger does not possess any toxic repercussions and side effects [10]. In a clinical trial study conducted on concentrated extracts of ginger revealed adverse gastrointestinal effects. The 65% of the enrolled responders reported eructation, dyspepsia or nausea. Diarrhea, heartburn and irritation of mouth also reported [11]. Some of the *in vitro* studies on ginger has indicated the inhibition of thromboxane synthesis and thereby, retarding platelet aggregation and increasing bleeding time [12]. Prolong bleeding time has adverse implications in injuries and in pregnant women [13]. But certain studies have revealed that consumption of ginger in pregnancy not only increases the risk of fetal death and reabsorption but it also impairs the normal process of implantation [14].

1.2 Quina *(Cinchona pubescens)*

Cinchona is also known as quina and red cinchona. It has been used in folk medicines for many uses like increasing appetite, improving digestion, treatment of bloating and other stomach problems. It is also used as antiarrhythmic, appetite stimulant, antipyretic and hepatoprotectives [15]. The bark of the plant is a rich source for quinine a popular antimalarial drug. Therefore, *Cinchona pubescens* is cultivated in tropical regions for the isolation of quinine. In spite of being effective in malaria, Cinchona bark has an unacceptable risk of toxicity resulting from the overdoses of quinine [16]. Quinine is linked to various biological side effects like allergic reactions, cardiotoxicity, anaemia, hypoglycaemia, cinchonism (headaches, visual problems, tinnitus, dizziness decrease in hearing acuity, diarrhea, nausea). These side effects mostly stems from the lack of optimization in dose of the quinine [17-19].

1.3 Ajwain *(Trachyspermum ammi)*

Ajwain *(Trachyspermum ammi)* is among the widely used and highly valued medicinal plant. It is an annual herb and is widely distributed in Pakistan.

It has been used in the treatment of digestive disorders and possess established antioxidant and neuro protective nature [9, 20, 21]. Ajwain is also reported to have aphrodisiac and diuretic nature [22]. It also owns antispasmodic and carminative properties and is used for flatulence, diarrhea, digestive stimulant, abdominal tumors, piles, reflux, hepato protective, nausea, vomiting, abdominal cramps, lack of appetite, hypolipidemic, asthma, antitussive and amenorrhea etc. [23-26]. On the other hand, toxicity of the plant is also reported. The oil of Ajwain was found to be moderately toxic [27]. But when it is taken in larger amounts it may result in allergic reactions, stomach ulcers, and liver and heart problems. Ajwain also indicated teratogenicity in rat fetuses. Therefore, its intake during pregnancy may result in adverse effects [26]. Furthermore, there is a risk of bleeding and bruising when taken in combination with certain other drugs. *T. ammi seeds can cause hepatotoxicity when it is supplemented with other herbs like Bishop›s* weed. It can also effect the platelet aggregation when taking in combination with herbs like garlic, ginkgo, turmeric etc. Headache and nausea are also reported due to overdose [28, 29].

1.4 Kinnikinnick *(Arctostaphylos uva-ursi)*

Arctostaphylos uva-ursi (L.) has gained significant importance in traditional medicine especially for the treatment of lower urinary tract infections[30]. Reports revealed the antimicrobial and antiseptic properties which are attributed to tannins and hydroquinones in the plant [31]. It is also reported to have significant amount of antioxidants [32]. It is also recommended for the treatment of dermatitis [33]. Clinical trial studies suggested some side effects of using the *uva-ursi*. Gastrointestinal problems are reported in some studies. Some researchers have reported dermal effects to the prolonged hydroquinone exposure found in *Arctostaphylos uva-ursi*. Blurred vision due to bull's-eye maculopathy is reported due to the prolong use of *uva-ursi* [34] Studies in rats indicated nephrotoxicity. [30, 35]. Stone formation is also reported after the use of *uva-ursi* [36].

1.5 Chamomile *(Matricaria chamomilla L.)*

Chamomile (*Matricaria chamomilla* L.) belongs to the family Asteraceae and often referred to as the "star among medicinal species"[37]. Its traditional uses have been documented in the ancient folkloric scriptures. It has been recommended in hysteria, flatulence, intermittent fever and colic. It is used as antiseptic, anti-inflammatory and antispasmodic. Some of the common uses are improving digestion and treating diarrhea, hemorrhoids, urinary tract problems, oral mucositis, shingles and painful menstruation [38-40]. Chamomile tea (CT)has stress relieving and nerve relaxant properties and has been used to remove inflammations, pain and to cure rheumatic disease [2, 41]. Conjunctivitis due to the external administration of Chamomile tea is reported as pollen of *M. chamomilla* may induce allergic reactions [42]. In addition, the use of chamomile taken with warfarin caused multiple internal hemorrhages [43]. The phytochemical nature of the Chamomile can led to various drug interactions. Chamomile may increase the effects of opioid analgesics that can cause CNS depression / sedation [44]. Regular intake of Chamomile can alter absorption of other drugs.

1.6 Ginseng *(Panax ginseng)*

Panax ginseng has been used in folk medicines since 2000 years. Word "Panax" corresponds to "all healing", which signifies the potential diverse therapeutic uses of this wonderful plant [45]. *P. ginseng* possess diverse pharmacological activities like being rich in antioxidants, possess anti-aging, hypolipidemic, hepatoprotective, anti-fatigue, anticancer, homeostasis and antihypertensive [46-48]. It is also used to improve the cognitive functions and aphrodisiac. It is also used as a general tonic for wellbeing. Ginseng based medicines are top selling herbal medicines [47]. In one of the study conducted on consumption of ginseng in pregnant women revealed increase up to 3 folds in gestational diabetes [49]. Moreover endocrinological manifestations like mastalgia and postmenopausal bleeding are reported with ginseng use which stopped after discontinuing the intake of ginseng [50]. Tachycardia and hypertension is also reported as a potential adverse effect of ginseng use [48]. Prolong use of ginseng may cause effects like diarrhea, skin eruption, insomnia, sleeplessness, nervousness, edema and decreased appetite [51]. Drug interactions of ginseng with imatinib in a leukemia patient resulting in liver toxicity is reported [52]. Potential interaction of ginseng with

warfarin is reported [53, 54]. Ginsenosides which are the active component of ginseng has the ability to inhibited platelet aggregation and therefore not recommended for patients undergoing surgical treatments [55-57].

1.7 Garlic *(Allium sativum)*

Commonly known as "garlic", *Allium sativum* has different uses in food and medicines. Pharmacognostic studies reveals diverse properties of garlic like antiviral, antimicrobial, anti-mutagenic, antihypertensive, anti-platelet, glucose lowering, antithrombotic etc. It is also used to treat hypercholesterolemia, cardiovascular diseases, dementia, hypertension, arteriosclerosis etc [58, 59]. On the other hand, the consumption of garlic can also cause numerous adverse effects. Orthostatic circulatory problems, acute myocardial infarction, food allergy has been described in some case studies as potential adverse effects of garlic [60-62]. Small intestinal obstruction, esophageal and epi-gastric pain, hematochezia and hematemesis, nausea, blotting and other gastrointestinal problems are reported [59]. Another case study revealed allergic dermatitis in patient who used garlic powder for treating hyperlipideamia. Urticaria, Angiedema another form of skin and mouth allergies are s also reported [63-65]. For pregnant and lactating mothers, the consumption of garlic should not exceed the doses normally used as in food. doses of garlic greatly exceeding amounts used in foods should not be taken during pregnancy and lactation [59]. Herb-drug interactions are common to garlic. Ritonavir an antiviral drug can manifest gastrointestinal toxicity, when administered with garlic supplements. Other antidiabetic and analgesics drugs can also interact with the garlic supplements [66, 67]. Mouth burns, upset stomach nausea, lightheadedness are some of the other concerns after ingestion of high amount of garlic [68].

1.8 Warmwood *(Artemesia absinthium)*

In local traditions *Artemesia absinthium* is used as febrifuge, anthelmintic, stomachic antiseptic, cardiac stimulant, antispasmodic, improving nervous and liver functions. In folkloric literatures, it is also described for neurodegenerative and ulcerogenic disease, dysentery and cancer [69]. *Artemesia absinthium* is known for the preparation of Absinthe (liqueur) that which has been banned due to toxic properties, resulting in hallucinations, mental disturbances, pyschosis, digestive disorders, delirium, vertigo, thirst, dyspepsia, biliary dyskinesia and paralysis etc. Their use for lactating mothers is strictly prohibited [68].

2. STANDARDIZATION & QUALITY ASSURANCE OF HERBAL MEDICINES

2.1 Authentication of Raw Material

Authentication of herb by the collector is the foremost and important step in the development cycle of herbal medicine preparation. Mostly, herbs are collected by the local people who actually are not trained enough, neither experts in identification of plant material. Sometimes, the plant material show striking similarities that makes taxonomic verification difficult for experts. The quality of raw material plays important role in the quality of the finished product. The authentication of the particular herb should be based on different tiers of identification. Authentication cycle should be based on verification of plant material on macro morphological features, microscopic level and molecular level. Therefore, a holistic approach is required for the correct identification of medicinal plant. Microscopic level identification can be performed by studying pollen morphologies through high resolution imaging techniques. In molecular approaches, DNA barcoding is applied as an efficient technique for identification of the raw material. DNA barcoding utilizes specific gene regions and identify the biological specimen based on conserved sequence data. The commonly used DNA markers or regions that are used in DNA barcoding are *rbcL, matK, trnh-psba*, or their combination [70, 71].

DNA barcoding technique can also be used to detect any adulterant plants in the finished product. In a recent study, different herbal preparations were tested to examine if the finished product contained the same herb as prescribed on the product labels. The examination revealed that 59% of the herbal medicines did not contained the exact herb written on the product label [72]. Herbal industries are suffering adversely due to the lack of proper quality control measures compromising the quality of herbal medicines. Product substations and

adulations are frequent in herbal industries which can be controlled using DNA barcoding.

2.1.2 Metal & Metalloids Adulterants

Healing and therapeutic properties of medicinal plants and herbs are attributed to their phytochemical components and minerals, however, plants may not only contain these. Several of non-essential minerals, toxic pollutants and heavy metals may be present in the plant [44]. Plants usually growing on the road sides, and those collected from polluted areas tends to accumulate heavy metals and other toxic substances. Furthermore, in cases where plants are grown in clean environment but the water reservoir is polluted with industrial effluents, and pesticides have also revealed accumulation of such toxic materials, which after ingestion can have lethal effects [73-75]. As, Ni, Pb, Al and Cd occurring in the environment can accumulate in both plants and human organs and are categorized as the most common heavy metals causing pollution by the Environment Protection Agency [76, 77]. In one of the recent article about herbal medicine market in Jordan, authors investigated herbs species for presentence of different heavy metals. Among the assessed plants, Pb (lead) was found beyond acceptable limits in one of the herb *Satureja thymbra*, also known as Persian thyme [77]. Similarly, there are different reports on the detection of pesticides like pendimethalin, carbendazim, procymidone, phoxim along with banned pesticides herbs chlorpyrifos and aldicarb [77]. The presence of such toxic and innocuous chemicals can cause server side effects and their long term exposure can be deadly. Some of these metals like As, Cd, Pbetc can cause cancer, poisoning, dermatitis, heart shock, kidney damage, osteoporosis etc [78]. Different strategies can be applied to overcome contamination like extensive clean-up steps, dilution, more selective detection techniques.

2.1.3 Microbial Contamination

One challenging aspects for the herbal industries are to meet proper and standardized biosafety assessments to check the potential of microbial contaminants in its products. Recently, one of the herbal manufacturing company (Herbalife®) came under the critics when different from different regions, there were reports of Herbalife® associated liver injury, initially reported in Israel, and afterwards Spain, Switzerland, Iceland, Argentina, and the United States [79]. Interestingly, no significant contamination with pesticides or heavy metals were found out, however, contamination with *Bacillus subtilis* in high amount having potential to cause hepatotoxicity was identified. Other reports, later on confirmed the presence of heavy metals and pathogenic microbes like *Streptococcus, Escherichia, Acinetobacter, Klebsiella*. Both the heavy metals and pathogens were identified as a cause of liver toxicity resulting from Herbalife® products [80-82].

2.2 Optimization of Dose & Phytochemistry

The adverse reactions from herbal medicines may arise from the particular herb and dosage but sometimes the lack of proper standardization of herbal medicines. Some medicinal plants if taken in lesser amounts can manifest their medicinal potential; however, at high doses they become poisonous. *Symphytum officinale* and *Corynanthe yohimbe* which are regarded as medicinal, aphrodisiac and dietary supplements can be lethal if taken in higher amounts [83]. The optimization of the dosage of herbal medicines should be carried out through ethno medicinal, pharmacological and clinical approaches, under different conditions, and on different samples. Some of the adverse effects of herbal medicines are reported if there is already a preexisting disease in the body. With the changing physiology of the body, the response to a herbal preparation can be different. Before using a medicinal plant preparation one has investigate the effective dose, ineffective doseand overdose.

The therapeutic potential of the medicinal plant is due to its phytochemistry which signifies the need of a standardized phytochemistry of plants. The phytochemistry of a same medicinal plant can change significantly with the change in environments and in response to different stress. At present, in most of the herbal industries, in the developing regions the phytochemical standardization of a herbal preparation is negligible. Plants are collected from different phytogeographical regions having a different phytochemical profile, thus hereby, compromises the quality of the product. Similarly, the phytochemical profiles changes with the change in the growing stages of the plant. Therefore, there is increasing interest in the tissue

culture based approaches like micro propagation to cultivate medicinal plants with relatively standardized phytochemistry. This also signifies the need of understanding the rich phytochemistry through efficient analytical techniques like HPLC fingerprinting.

3. CONCLUSION

Herbal medicines play a very important part in fulfilling the health vacuum since ancient times. A massive chunk of human population relies on the folkloric traditions for treatment. The narrative of herbs being always safe is misleading that signifies the need to significant research on the safety and efficacy of herbal medicines. It's difficult to separate a medicinal plant from potentially poisonous plants. Sometimes, the adverse effects stems from the lack of quality control measures. False identification, adulteration, heavy metal contamination, herb drug interaction are some of the causes of adverse effectsand compromises the quality of herbal medicines. Research on the standardization procedures, pharmacology, drug interactions, dose optimization etc. will significantly help in reducing the risk with the use of herbal medicines. In addition, good manufacturing practices must be at the core of any herbal industry. A holistic approach is required to tackle the industry related issues. Policy measures and stringent laws for the registration of herbal medicines can be made so that herbal products with unlabeled and uncharacterized ingredients, inconsistent standard manufacturing can be dealt with.

4. Conflict of interests

Authors declare no conflict of interest.

5. REFERENCES

1. Knöss, W., Toxicity of herbal medicines: From past to present to future, Toxicology of Herbal Products, *Springer* 1-9 (2013).
2. Srivastava, J.K., E.Shankar, & S. Gupta, Chamomile: A herbal medicine of the past with a bright future, *Molecular Medicine Reports,* 3: 895-901(2010).
3. Yang, B., Y. Xie, M. Guo, M.H. Rosner, H. Yang, & C. Ronco, Nephrotoxicity and Chinese herbal medicine, *Clinical Journal of the American Society of Nephrology,* 13:1605-1611(2018).
4. Khalil, A.T., Z.K. Shinwari, M. Qaiser, & K.B. Marwat, Phyto-therapeutic claims about euphorbeaceous plants belonging to Pakistan; an ethnomedicinal review, *Pak. J. Bot*, 46: 1137-1144(2014).
5. George, P., Concerns regarding the safety and toxicity of medicinal plants-An overview, *Journal of Applied Pharmaceutical Science,* 1: 40-44 (2011).
6. Serrano, R., Toxic Plants: Knowledge, Medicinal Uses and Potential Human Health Risks, *Environment and Ecology Research*, 6: 487-492 (2018),.
7. Kane, J., S. Kane, & S. Jain, Hepatitis induced by traditional Chinese herbs; possible toxic components, *Gut,* 36: 146-147 (1995).
8. Kazemipoor, M., C. W. M. Radzi, G.A. Cordell, & I. Yaze, Safety, efficacy and metabolism of traditional medicinal plants in the management of obesity: a review, *International Journal of Chemical Engineering and Applications,* 3: 288-292(2012).
9. Jan, S.A., Z.K. Shinwari, A. Zeb, A.T. Khalil, & S.H. Shah, Ethnobotany and research trends in *Trachyspermum ammi* L.(Ajowan); A popular folklore remedy, *American-Eurasian Journal of Agricultural & Environmental Sciences*, 15: 68-73(2015).
10. Phillips, S., R. Ruggier, & S. Hutchinson, *Zingiber officinale* (ginger)–an antiemetic for day case surgery, *Anaesthesia, 48*: 715-717 (1993).
11. Altman, R.D., & K. Marcussen, Effects of a ginger extract on knee pain in patients with osteoarthritis, Arthritis & Rheumatism, 44 : 2531-2538(2001).
12. Srivastava, K., Effects of aqueous extracts of onion, garlic and ginger on platelet aggregation and metabolism of arachidonic acid in the blood vascular system: in vitro study, Prostaglandins, Leukotrienes and Medicine, 13: 227-235(1984).
13. Miller, L.G., Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions, *Archives of internal medicine,* 158 : 2200-2211(1998).
14. Pollak, P.T., Herbal Cardiotoxicity: Can Mother Nature Hurt the Heart?, *Canadian Journal of Cardiology,* 32: 291-293(2016).
15. Noriega, P., M. Sola, A. Barukcic, K. Garcia, & E. Osorio, Cosmetic antioxidant potential of extracts from species of the *Cinchona pubescens* (Vahl), *Int J Phytocosm Nat Ing,* 2: 1-14(2015).
16. Räth, K., K. Taxis, G. Walz, C.H. Gleiter, S.-M. Li, & L. Heide, Pharmacokinetic study of artemisinin after oral intake of a traditional preparation of *Artemisia annua* L.(annual wormwood), *The American journal of tropical medicine and hygiene,* 70:128-132 (2004).
17. Ogetii, G.N., S. Akech, J. Jemutai, M. Boga, E. Kivaya, G. Fegan, & K. Maitland, Hypoglycaemia in severe malaria, clinical associations and relationship to quinine dosage, *BMC infectious diseases,* 10: 334(2010.
18. Tumwikirize, W., J. Ogwal-Okeng, A. Vernby,

W. Anokbonggo, L. Gustafsson, & S. Lundborg, Adverse drug reactions in patients admitted on internal medicine wards in a district and regional hospital in Uganda, A*frican health sciences,* 11 (2011).
19. Danno, K., F. Rerolle, S. de Sigalony, A. Colas, L. Terzan, & M.-F. Bordet, China rubra for side-effects of quinine: a prospective, randomised study in pregnant women with malaria in Cotonou, Benin, *Homeopathy,* 103:165-171 (2014).
20. Farzaei, M.H., M.M. Zangeneh, N. Goodarzi, & A. Zangeneh, Stereological Assessment of Nephroprotective Effects of Trachyspermum ammi Essential Oil against Carbon Tetrachloride-Induced Nephrotoxicity in Mice, *International Journal of Morphology,* 36 (2018).
21. Izadpanah, S., A.H. Abdolghaffari, F. Farjadmand, M. Eftekhari, M. Baeeri, M. Rahimifard, S. Momtaz, M. Abdollahi, R. Rahimi, & M.R.S. Ardekani, Beneficial Effects of *Trachyspermum ammi* (L.) Sprague on Rat Irritable Bowel Syndrome, *Research Journal of Pharmacognosy (RJP)*, 6: 57-66(2019).
22. Bairwa, R., R. Sodha, & B. Rajawat, *Trachyspermum ammi*, *Pharmacognosy reviews,* 6: 56(2012).
23. Krishnamoorthy, V., & M. Madalageri, Bishop weeds (*Trachyspermum ammi*): An essential crop for north Karnatka, *Journal of Medicinal and Aromatic Plant Sciences,* 21: 996-998(1999).
24. Vasudevan, K., S. Vembar, K. Veeraraghavan, & P. Haranath, Influence of intragastric perfusion of aqueous spice extracts on acid secretion in anesthetized albino rats, *Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology,* 19: 53-56 (2000).
25. Chialva, F., F. Monguzzi, P. Manitto, A. Akgül, Essential oil constituents of Trachyspermum copticum (L.) Link fruits, *Journal of essential oil research*, 5 :105-106(1993).
26. Zarshenas, M.M., M. Moein, S.M. Samani, & P. Petramfar, An overview on ajwain (*Trachyspermum ammi)* pharmacological effects; modern and traditional, *Journal of natural Remedies*, 1: 98-105 (2013).
27. Vazirian, M., D. Hekmati, S. Ostad, & A. Manayi, Toxicity Evaluation of Essential oil of *Trachyspermum ammi* in Acute and Sub-chronic Toxicity Experiments, *Journal of Medicinal Plants,* 1: 70-77(2018).
28. Grossberg, G.T., & B. Fox, The essential herb-drug-vitamin interaction guide: the safe way to use medications and supplements together, *Harmony (*2008).
29. Asif, H.M., S. Sultana, N. Akhtar, A panoramic view on phytochemical, nutritional, ethanobotanical uses and pharmacological values of *Trachyspermum ammi* Linn, *Asian Pacific Journal of Tropical Biomedicine,* 4: S545-S553(2014).
30. de Arriba, S.G., B. Naser, & K.-U. Nolte, Risk assessment of free hydroquinone derived from Arctostaphylos Uva-ursi folium herbal preparations, *International journal of toxicology,* 32: 442-453 (2013).
31. Afshar, K., N. Fleischmann, G. Schmiemann, J. Bleidorn, E. Hummers-Pradier, T. Friede, K. Wegscheider, M. Moore, & I. Gágyor, Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with *uva-ursi* (REGATTA)–a double-blind, randomized, controlled comparative effectiveness trial, *BMC complementary and alternative medicine,* 18: 203(2018).
32. Shaffique, S., A. Rehman, S. Ahmad, H. Anwer, H.M. Asif, G. Husain, T. Rehman, & S. Javed, A Panoramic Review on Ethnobotanical, Phytochemical, Pharmacological and Homeopathic Uses of Echinacea angustifolia, *RADS Journal of Pharmacy and Pharmaceutical Sciences,* 6: 282-286(2018).
33. Saeed, F., N. Jahan, & M. Ahmad, In vivo evaluation & safety profile evaluation of *Arctostaphylos uva-ursi* (L.) Spreng. extract in rabbits, *Pakistan journal of pharmaceutical sciences*, 27 (2014).
34. Wang, L., L.V. & Del Priore, Bull's-eye maculopathy secondary to herbal toxicity from uva ursi, *American journal of ophthalmology,* 137 :1135-1137(2004).
35. Larsson, B., A. Jonasson, & S. Fianu, Prophylactic effect of UVA-E in women with recurrent cystitis: a preliminary report, Current therapeutic research, 53: 441-443(1993).
36. Fatima, N., & N. Nayeem, Toxic effects as a result of herbal medicine intake, Toxicology-New Aspects to This Scientific Conundrum, *IntechOpen* (2016).
37. Singh, O., Z. Khanam, N. Misra, & M.K. Srivastava, Chamomile *(Matricaria chamomilla* L.): an overview, *Pharmacognosy reviews,* 5: 82 (2011).
38. Tyihak, E., J. Sarkany-Kiss, & G. Verzar-Petri, Phytochemical investigation of apigenin glycosides of Matricaria chamomilla, *Pharmazie,* 17: 301-304(1962).
39. Mericli, A.H., The lipophilic compounds of a Turkish Matricaria chamomilla variety with no chamazulene in the volatile oil, *International Journal of Crude Drug Research,* 28:145-147(1990).
40. Mazokopakis, E., G. Vrentzos, J. Papadakis, D. Babalis, & E. Ganotakis, Wild chamomile (*Matricaria recutita* L.) mouthwashes in methotrexate-induced oral mucositis, Phytomedicine, 12: 25-27 (2005).
41. McKay, D.L., & J.B. Blumberg, A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.), Phytotherapy Research: An *International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives,* 20: 519-530 (2006).
42. Subiza, J., J. Subiza, M. Alonso, M. Hinojosa, R. Garcia, M. Jerez, & E. Subiza, Allergic conjunctivitis to chamomile tea, *Annals of allergy,* 65: 127-132(1990).

43. Segal, R., & L. Pilote, Warfarin interaction with Matricaria chamomilla, *Cmaj,* 174: 1281-1282 (2006).
44. Abebe, W., Herbal medication: potential for adverse interactions with analgesic drugs, *Journal of clinical pharmacy and therapeutics*, 27: 391-401(2002).
45. Lee, C.H., & J.-H. Kim, A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases, *Journal of Ginseng Research,* 38 161-166(2014).
46. Bae, S.J., G.J. Rho, K.M. Kim, & J.S. Kang, Pharmacological effects of active saponins from Panax ginseng Meyer, *Tropical Journal of Pharmaceutical Research*, 18 (2019).
47. Ernst, E., Panax ginseng: an overview of the clinical evidence, *Journal of Ginseng Research,* 34: 259-263(2010).
48. O'Hara, M., D. Kiefer, K. Farrell, & K. Kemper, A review of 12 commonly used medicinal herbs, *Archives of Family Medicine*, 7: 523(1998).
49. Chin, R.K., Ginseng and common pregnancy disorders, *Asia-Oceania Journal of Obstetrics and Gynaecology*, 17: 379-380(1991).
50. Dukes, M., *Ginseng* and mastalgia, *British medical journal*, 1: 1621(1978).
51. D.J. Paik, C.H. Lee, Review of cases of patient risk associated with *ginseng* abuse and misuse, *Journal of Ginseng Research,* 39: 89-93(2015).
52. Bilgi, N., K. Bell, A.N. Ananthakrishnan, & E. Atallah, Imatinib and Panax ginseng: a potential interaction resulting in liver toxicity, *Annals of Pharmacotherapy,* 44: 926-928 (2010).
53. Zhu, M., K. Chan, L. Ng, Q. Chang, S. Chang, & R. Li, Possible influences of ginseng on the pharmacokinetics and pharmacodynamics of warfarin in rats, *Journal of pharmacy and pharmacology,* 51: 175-180 (1999).
54. Yuan, C.-S., G. Wei, L. Dey, T. Karrison, L. Nahlik, S. Maleckar, K. Kasza, M. Ang-Lee, & J. Moss, Brief communication: American ginseng reduces warfarin's effect in healthy patients, *Ann Intern Med*, 141: 23-27 (2004).
55. Kuo, S.-C., C.-M. Teng, J.-C. Lee, F.-N. Ko, S.-C. Chen, & T.-S.Wu, Antiplatelet components in *Panex ginseng,* Planta medica, 56: 164-167(1990).
56. Lee, J.G., Y.Y. Lee, S.Y. Kim, J.S. Pyo, H.S. Yun-Choi, & J.H. Park, Platelet antiaggregating activity of ginsenosides isolated from processed ginseng, Die *Pharmazie-An International Journal of Pharmaceutical Sciences,* 64: 602-604(2009).
57. JLee, .G., Y.Y. Lee, B. Wu, S.Y. Kim, Y.J. Lee, H.S. Yun-Choi, & J.H. Park, Inhibitory activity of ginsenosides isolated from processed ginseng on platelet aggregation, *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, 65: 520-522(2010).
58. Bongiorno, P.B., P.M. Fratellone,& P. LoGiudice, Potential health benefits of garlic (*Allium sativum*): a narrative review, *Journal of Complementary and Integrative Medicine,* 5 (2008).
59. Borrelli, F., R. Capasso, A.A. Izzo, Garlic (Allium sativum L.): adverse effects and drug interactions in humans, Molecular nutrition & food research, 51 (2007) 1386-1397.
60. Beck, E., & J. Grunwald, *ALLIUM sativum* IN DER STUFENTHERAPIE DER HYPERLIPIDAMIE: STUDIE MIT 1997 PATIENTEN BELEGT WIRKSAMKEIT UND VERTRAGLICHKEIT, *Medizinische Welt*, 44 516-520(1993).
61. Gupta, M.K., S. Mittal, A.K. Mathur, & A.K. Bhan, Garlic—the other side of the coin, *International journal of cardiology,* 38:333 (1993).
62. Benes, J., K. Prerovský, L. Rehůrek, & F. Kase, Garlic food allergy with symptoms of Meniere's disease, Casopis lekaru ceskych, 105: 825-827(1966).
63. Burden, A., S. Wilkinson, M. Beck, & R. Chalmers, Garlic-induced systemic contact dermatitis, Contact Dermatitis, 30: 299-300(1994).
64. Pires, G., E. Pargana, V. Loureiro, M. Almeida, & J. Pinto, Allergy to garlic, *Allergy*, 57: 957-958(2002).
65. Sanchez-Hernandez, M., M. Hernandez, J. Delgado, P. Guardia, J. Monteseirin, B. Bartolomé, R. Palacios, J. Martinez, & J. Conde, Allergenic cross-reactivity in the Liliaceae family, *Allergy*, 55: 297-299(2000).
66. Saw, J.T., M.B. Bahari, H.H. Ang, & Y.H. Lim, Potential drug–herb interaction with antiplatelet/ anticoagulant drugs, Complementary therapies in clinical practice, 12: 236-241(2006).
67. Laroche, M., S. Choudhri, K. Gallicano, & B. Foster, Severe gastrointestinal toxicity with concomitant ingestion of ritonavir and garlic, *Can J Infect Dis,* 9 471P(1998).
68. Poppenga, R.H., Herbal medicine: potential for intoxication and interactions with conventional drugs, *Clinical techniques in small animal practice,* 17: 6-18(2002).
69. Bora, K.S., A. Sharma, Phytochemical and pharmacological potential of Artemisia absinthium Linn. and Artemisia asiatica Nakai: a review, J Pharm Res, 3 (2010) 325-328.
70. Zahra, N.B., Z.K. Shinwari, & M. Qaiser, Dna barcoding: a tool for standardization of Herbal Medicinal Products (HMPS) of *Lamiaceae* From Pakistan, *Pakistan Journal of Botany,* 48: 2167-2174(2016).
71. Shinwari, Z.K., S.A. Jan, A.T. Khalil, A. Khan, M. Ali, M. Qaiser, & N.B. Zahra, Identification and phylogenetic analysis of selected medicinal plant species from pakistan: dna barcoding approach, *Pak. J. Bot,* 50:553-560(2018).
72. Newmaster, S.G., M. Grguric, D. Shanmughanandhan, S. Ramalingam, & S.

Ragupathy, DNA barcoding detects contamination and substitution in North American herbal products, *BMC medicine,* 11: 222(2013).

73. Abou-Arab, A., & M. Abou Donia, Heavy metals in Egyptian spices and medicinal plants and the effect of processing on their levels, *Journal of agricultural and food chemistry,* 48: 2300-2304(2000).
74. Pethkar, A., R. Gaikaiwari, & K. Paknikar, Biosorptive removal of contaminating heavy metals from plant extracts of medicinal value, *Current Science,* 80:1216-1218(2001).
75. Khan, Z.I., K. Ahmad, M.J.Z. Rasheed, R. Nawaz, M. Ayub, A.F. Zahoor, A. Anjum, M. Yousaf, Z.U.H. Dogar, & K.U. Rahman, Toxic and some essential metals in medicinal plants used in herbal medicines: a case study in Pakistan, *African Journal of Pharmacy and Pharmacology*, 7: 1389-1395(2013).
76. Başgel, S., & S. Erdemoğlu, Determination of mineral and trace elements in some medicinal herbs and their infusions consumed in Turkey, *Science of the total environment*, 359: 82-89(2006).
77. Alhusban, A.A., S.A. Ata, & S.A. Shraim, The safety assessment of toxic metals in commonly used pharmaceutical herbal products and traditional herbs for infants in Jordanian market, *Biological trace element research,* 187: 307-315(2019).
78. Gyamfi, E.T., Metals and metalloids in traditional medicines (Ayurvedic medicines, nutraceuticals and traditional Chinese medicines), *Environmental Science and Pollution Research,* 1-12 (2019).
79. Teschke, R., C. Frenzel, J. Schulze, A. Schwarzenboeck, & A. Eickhoff, Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests, World *journal of hepatology,* 5: 353(2013).
80. Stickel, F., S. Droz, E. Patsenker, K. Bögli-Stuber, B. Aebi, & S.L. Leib, Severe hepatotoxicity following ingestion of Herbalife® nutritional supplements contaminated with Bacillus subtilis, *Journal of hepatology*, 50: 111-117(2009).
81. Jaishankar, M., T. Tseten, N. Anbalagan, B.B. Mathew, & K.N. Beeregowda, Toxicity, mechanism and health effects of some heavy metals, Interdisciplinary toxicology, 7: 60-72 (2014).
82. Philips, C.A., P. Augustine, S. Rajesh, S.K. John, G.C. Valiathan, J. Mathew, S. Phalke, & K.L. Antony, Slimming to the Death: Herbalife®-Associated Fatal Acute Liver Failure—Heavy Metals, Toxic Compounds, Bacterial Contaminants and Psychotropic Agents in Products Sold in India, *Journal of clinical and experimental hepatology*, 9: 268-272(2019).
83. Gurib-Fakim, A., Medicinal plants: traditions of yesterday and drugs of tomorrow, *Molecular aspects of Medicine*, 27: 1-93(2006).