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Review on pesticide residue analytical methods and residue status in medicinal plants

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Abstract
Medicinal plants are consumed worldwide for the treatment of several diseases and are important raw materials for the production of photochemical by pharmaceutical industries. The medicinal plant is susceptible to wide ranges of pests and diseases, which causes economic crop loss as well as quality of herbal products and is often treated with chemical pesticides to manage these problems. The presence of trace level of pesticide residues in the herbal plants, which impose serious health risks to human health. Several studies have been reported the presence of pesticide residues in medicinal plants and their preparations. This review is conducted to provide different analytical methods for analysis of pesticide residues and residue status in the medicinal plants.

Keywords: Medicinal plants, analytical methods, residues

Introduction
India has the most diverse cultural traditions in the use of medicinal plants and it harbours around 17000-18000 species of flowering plants of which 6000-7000 are estimated to have medicinal usage in folk and documented systems of medicines like Ayurveda, Siddha, Unani and Homoeopathy [1]. India regularly exports 40-50 thousand tonnes of dried herbs and plant parts to the western world in addition to the local and household consumption of 27-28 thousand tonnes /year [2]. According to the report of World Health Organization (WHO) more than 80 % of the world's population relies on traditional medicine, mainly of plant base, in their primary healthcare [3]. The medicinal values of these plants are usually due to the presence of phytochemical constituent as stated by Essien *et al*. [4] and the most important of these phytochemicals include alkaloids, flavonoids, tannins, sapnonis, glycosides, essential fatty acids, bitter substances and phenolic compounds. Medicinal plants are the local heritage with global importance, World is endowed with a rich wealth of medicinal plants. With the ever-increasing worldwide use of herbal medicines and the rapid expansion of their global market, the safety and quality of medicinal plant materials and finished herbal medicinal products has become a major concern for health authorities, pharmaceutical industries and the public.

The demand for medicinal plants is increasing due to their usage both as a source of active ingredients for modern medicine [5] as well as for producing herbal products while providing a viable business opportunity to entrepreneurs [6]. The ever increasing consumption of medicinal plants necessitates large scale cultivation of medicinal plants which is impractical without use of pesticides [7]. The medicinal plant is attacked by several pests and diseases and it is imperative that plant protection chemicals are applied to reduce the severity of infestation. Among the factors limiting the quality and quantity of medicinal plant tea production, the role of insect pests is important. As a result, the tea planters use a wide range of pesticides to combat these problems for high yield and economic returns. In recent years, a number of research papers have dealt with the presence of different pesticides in medicinal plants have also been reported. Contamination of crude medicinal plants as well as their products with pesticide residue has been increasingly reported [5, 8-9]. Even though there are many number of published information on toxicity due to the presence of pesticides and fumigants, in the herbs and herbal products are free of these chemicals or at least ensure the absence of unsafe levels of residue [10]. The presence of pesticide residues in herbal materials can adversely affect the development and process of internationalization of traditional herbal medicine. The present review is focusing on analytical method and residue status in medicinal plants.

Pesticide residue analysis in medicinal plants

To detect low concentrations of pesticide residues, highly selective, sensitive and accurate analytical methods are needed. There are several reports published on the analysis of pesticides in crude medicinal plants such as organochlorines (OCs) [8, 11-12], organophosphorus (OP) [13-14] and their preparations [15]. However, most conventional methodologies for pesticide residue analysis of medicinal plants and their products, such as the European Pharmacopeia (EP) procedure, are costly, time-consuming and require large samples and greater volumes of hazardous solvents [16]. An indispensable requisite to ensure quality and reliability of the results in chemical analysis is method validation. The analyst must produce information to demonstrate that a method intended for this purpose is capable of offering adequate specificity, accuracy, and precision, at relevant analyte concentrations and in appropriate matrices. Sample preparation of multiresidues analysis is normally required to isolate and concentrate com-pounds of interest from the sample matrix prior to chromatography analysis. The methodologies used in the analysis of the different food samples involve (i) homogenization of samples, (ii) extraction of the samples into a suitable organic solvent, (iii) cleanup of the solvent extract and (iv) analysis of the cleaned-up extract with gas chromatography (GC) instrumentation, using specific detectors and GC-mass spectrometry (MS) [17].

The official multiresidue pesticide methods recommend extraction of the pesticides with organic solvents like hexane: dichloromethane [8], hexane [18-19], acetone: petroleum ether [20-21] hexane/diethyl ether/acetone [22], n-hexane and acetone [23], acetonitrile [24-26] and ethyl acetate [27], clean-up by dispersive solid-phase extraction clean [25-32], column chromatography [23] and quantification by GC [29, 33-36] or GC-MS [26-27, 37-42] and LC-MS [43-44]. A variety of classical sample preparation methods, such as solid-liquid extraction (SLE)[6], matrix solid-phase dispersion (MSPD) [11, 16, 22], solid phase extraction (SPE) [45], solid phase microextraction (SPME) associated with microwave assisted extraction (MAE) [46] and Ultrasound-Assisted Dispersive Liquid-Liquid Microextraction (UA-DLLME) [14] were widely used to determine pesticide residues in medicinal plants. The QuEChERS (quick, easy, cheap, effective, rugged and safe) method, developed originally for the determination of pesticide residues in food of plant origin, can be also an attractive alternative for analysis of organic contaminants such as mycotoxins, drugs, veterinary medicines, and finally, Polycyclic aromatic hydrocarbons (PAHs). As yet, the QuEChERS method has been applied recently to the study of pesticide residues in herbal plants [26, 29, 31-33, 40, 42, 47].

Pesticide residues in medicinal plants

Recently, studies have noted the presence of pesticide residues in medicinal plants used for preparation of phytomedicines. High incidence of organochlorines (OCs) pesticide residues has been reported in traditional Chinese [48], Brazilian [8, 11], Indian [19] and Egyptian [49] medicinal herbs. Another recent study has revealed the presence of organophosphorus pesticides in medicinal plants commonly consumed in Iran [13]. Some countries have established national requirements for maximum residue limits in medicinal herbs of regions wherein most of the accepted limits are extrapolated from the limits (Table 1) established for food commodities [50].

Table 1: Examples of national limits set for various pesticide residues [50]

Pesticides	Limit (mg/kg)
	EP[a], USP[c] and FA[c]
DDT and its isomer (op-DDT, pp- DDD, pp-DDE and pp-DDT)	1.0
Chlordane (sum of cis, trans and oxythlordane)	0.05
Aldrin and dieldrin (sum of)	0.05
Endosulfan (sum of isomers and endosulfan sulfate)	3.0
Endrin	0.05
Heptachlor (sum of heptachlor and heptachlorepoxide)	0.05
Hexachlorobenzene	0.1
HCH (sum of α, β, γ and δ)	0.6 (γ), 0.3 other
Azinphos-methyl	1.0
Bromopropylate	3.0
Chlorfenvinphos	0.5
Chlorpyriphos methyl	0.1
Diazinon	0.5
Dichlorvos	1.0
Ethion	2.0
Fenitrothion	0.5
Fonofos	0.05
Phosalone	0.1
Cypermethrin	1.0
Fenvalerate	1.5

EP- European Pharmacopoeia, FA- Pharmacopeia Argentina, USP- United States Pharmacopeia

[a]Applicable to medicinal plant materials included in the European pharmacopoeia, 5th ed, unless otherwise indicated in the applicable monograph. Reference: PHARMEUROPA Volume 18, No. 4, October 2006.

[c]Values in United States pharmacopeia28 and Argentina pharmacopoeia, Vol. 1

Several studies have been conducted worldwide to determine the pesticide residues in raw medicinal herbs (Table 2). Among the different pesticide groups, the presence of OCs pesticide residues in medicinal plants has been commonly reported [8, 12, 20, 23, 51]. The high incidence of OCs pesticide residues has been reported in traditional Chinese [20, 48, 52], Brazilian [8] and Egyptian [53] medicinal herbs. Various research studies have revealed the presence of banned OCs in American ginseng [33], Panax ginseng [51], Radix sp. [52, 54] and commercial ginseng root products [27, 39] that are consumed as dietary supplements. Although India is a major biodiversity centre for medicinal herbs, very few studies have been conducted to determine the presence of pesticide residues in medicinal crops. There are some reports of high levels of hexachlorocyclohexane (HCH) residues in the popular medicinal plant, viz., *Withania somnifera* (L.) of Indian System of Medicine (ISM) [16] and dashmool plant samples [19]. A total of 40 samples of single crude drugs (Dashmool) were checked for the presence of OC pesticide residues and its different metabolites of DDT, DDE, isomers of HCH and α- endosulfan. Results indicated that only 5% contain residue of DDT or its metabolites. However, presence of α-HCH and γ-HCH, the main constituents of commercial HCH was detected in 97.5% samples [19].

Most studies still revealed the high incidence of OCs pesticides in several herbal drugs worldwide [11, 16, 20, 52, 55-56].

The occurrence of banned OCs is accentuated when determining pesticide occurrence in commodities based on roots principally due to the cultivation in contaminated soils with several decades of agricultural use [27, 33, 39, 52, 54]. Additional interest lies on OCs residues in those commodities which are consumed with dietary supplement purpose such as Ginseng root powders [39]. Other authors reported residues of carbendazim, cyazofamid, diethofencarb and pyrimethanil in Asian Ginseng [58]. A total of 224 Korean herb samples (including *A. senticosus, M. alba* L., and *H. dulcis*) were collected from domestic markets from December 2007 till March 2009 and analyzed for the presence of pesticide residue [40]. Of which, 11samples (4.9%) were found to be positive with pesticides such as chlorfenapyr, chlorfluazuron, cyhalotrin, metalaxyl, pyridalyl, fenvalerate, tebuconazole, pp′-DDE, sanmarton and tebufenozide, however, all found pesticides were under their MRLs. It is necessary to point out that the pp′-DDE was founded in one sample and this pesticide belongs to the chlorinated pesticide group and is a product of the breakdown of DDT, a banned pesticide for agricultural use worldwide under the Stockholm Convention [40].

Table 2: Analytical method and pesticide residues in medicinal plants

Pesticides	Substrates	Determination	LOQ (mg/kg)	Residue level (mg/kg)	Reference
6 Carbamates (metolcarb, isoprocarb, fenobucarb, carbofuran, pirimicarb, and carbaryl)	Traditional Chinese herbs	GC-NPD	0.05	-	Wu *et al*. 2005 [35]
18 OCs	Tradtional Chinese medicine	GC-ECD	0.0004-0.009	0.0004-0.01	Hao and Xue (2006) [12]
18 OCs	10 Traditional Chinese Plants	GC-ECD	-	0.001-0.078	Sun *et al*. (2007) [20]
53 multi-class pesticides	6 traditional Chinese herbs	GC-MS (SIM)	0.01	-	Miao *et al*. (2010) [43]
74 multi-class pesticides	6 traditional Chinese herbs	LC-(QqQ)MS/MS	0.01	-	Mao *et al*. (2010) [60]
16 OPs	4 Chinese herbs	GC-FPD	0.001-0.009	0.002-0.01	Wan *et al*. 2010 [61]
195 Multi-class pesticides	Traditional Chinese herbs	GC-MS (SIM)	0.0025-0.05	-	Wang *et al*. 2011 [41]
14 OCs	Traditional medicine	GC-ECD	-	0.005-0.082	Agbeve *et al*. (2014) [23]
9OCs	Leaves of Mikania laevigata, Maytenus ilicifolia and Cordia verbenacea	GC-MS	0.002-0.03	0.002-0.11	Rodrigues *et al*. (2007 [8]
163 (6 acaricides, 62 fungicides, 18 herbicides and 77 insecticides)	chamomile, linden, melissa, peppermint and thyme	GC-ECD	0.005-0.04	0.02-0.21	Łozowicka *et al*. (2014) [22]
19 OCs	Ginseng	GC-MS	0.01	0.01-0.04	Zhi-Guang *et al*. (2011) [51]
18 multi-class (fungicides, insecticides)	Ginseng root	GC-ECD/NPD	0.003-.02	-	Park *et al*. 2007 [34]
108 OPs pesticides	Ginseng root	GC-MS (SIM) GC-FPD	0.025 - 5.0	0.025	Wong *et al*. (2007) [47]
35 pesticides	Basil, tarragon, sage, lovage, mint, parsley, rosemary and oregano.	GC-SIM-MS	0.001-0.012	0.001-0.04	Sadowska-Rociek *et al*. (2013) [28]
18 pesticides	medicinal herbs	GC-ECD/NPD	-	0.034- 0.579	Oh (2007) [24]
47 pesticides	medicinal herbs	GC-ECD/NPD	-	0.044-0.501	Oh (2009) [58]
81 multiclass pesticides	Ginkgo leaves	GC-MS (SIM)	0.0016-0.058	-	Zhou *et al*. (2011) [42]
234 pesticides	Korean herbs	GC-MS (SIM)	0.006-0.075	0.08-0.60	Nguyen *et al*. (2010) [40]

Among 292 samples, eight Chinese and one Korean HDMs were contaminated with five pesticides such as methoxychlor, DDT, γ-BHC, endosulfan and procymidone (0.044-0.501 mg/kg). The detection rate of pesticides in the tested HDMs was determined as 3.1%. On critical observation of the detected amount of procymidone (0.501 mg/kg) and methoxychlor (0.382 and 0.312 mg/kg), further intensive monitoring of the pesticides might be necessary for HDM [58] (Oh 2009). Other studies showed that, from the 8 detected pesticides (residues between 0.034- 0.579 mg/kg), 4 of them were fungicides (captan, chinomethionate, procymidone and tolyfluanid) [24]. Moreover, major residues of chlorothalonil fungicide were also detected in Brazilian Passiflora L. leaves [11]. In order to reduce health risks from residual pesticides in herbal drug products, the residue information of pesticides should be acquired. Therefore, 38 commodities (229 herbal crude drug materials) were analyzed for 44 different pesticides. Among the 229 samples (36 types of herbal crude drugs), seven imported and two domestic drug materials were contaminated with eight pesticides (0.034 to 0.579 mg/kg) such as BHC, procymidone, endosulfan, etc. Among the eight detected pesticides, four were fungicides, which were found in underground crude drug materials such as rhizoma or radix [24]. Levels of 14 organochlorine pesticide residues were evaluated in 127 samples of medicinal plants collected in pharmacies (78 samples) and herb stores (49

samples) in 1996 In Portugal [18]. Most samples sold in pharmacies contained residues of γ-HCH (51.3%). All residues were detected in analyzed samples, with exception of endrin in herb store samples. Detection frequency varied between 51.3% for γ-HCH and 1.3% for endrin in pharmacy samples, and between 34.7% for HCB and 4.1% for endosulfan sulfate in herb store samples. Maximum residue levels were exceeded in 38 (48.7%) pharmacy samples and in 26 (53.1%) medicinal herb store samples. The results showed that 24 samples (80%) contained pesticides above the detection limit and 13 samples (43%) did not comply with the maximum residue limits (MRL) for total quintozene, hexachlorobenzene, total hexachlorocyclohexane, lindane, total heptachlor, e-chlorpyrifos and folpet, imposed for botanical extracts. Total quintozene, hexachlorobenzene, total hexachlorocyclohexane and lindane were present in all contaminated samples and exceeded the MRL in eleven samples, with levels up to 55 and 30 times their respective MRL [59].

Xue *et al*. [21] analyzed 280 samples of 30 different traditional Chinese medicines (TCMs) to determine levels of contamination with OC pesticides and the results showed that 75.8% of samples contained at least one of the studied pesticides. More than 50% of samples contained α-BHC (55.8%) and PCNB (55.8%); hexachlorobenzene was detected in 40.9% of samples, tecnazene in 19.5%,γ-BHC in 16.7% and p,p'-DDE in 16.0%. Less than 10% of samples contained β-BHC, δ-BHC, heptachlor, aldrin, o, p' -DDT, p,p' -DDT and p, p'-DDD. None of the 280 samples contained heptachlor epoxide, MPCPS, α-endosulfan, trans chlorodane, or cis-chlorodane. Concentrations of OCs in four samples exceeded the maximum allowable residue limits (MRLs) specified in the PRC Pharmacopoeia 2005. The results indicate that the most common contaminants among the 280 samples were α-BHC, PCNB, hexachlorobenzene, and tecnazene. Park *et al*. [34] collected the ginseng root samples in the Korean, high concentrations (1.6 mg/kg) of tolclofos-m were detected in all samples. Although the pesticide was detected, the level was lower than the MRL established by KFDA, except in the case of one sample. Contamination of the area and the use of pesticides for the treatment of ginseng have had a marked influence on the concentration of contaminants found in ginseng. Interestingly, in a recent study[25] on traditional Chinese medicinal plants in the United States, high concentrations of chlorpyrifos were detected in 25% samples. Interestingly, the samples collected from the wild sources contained a higher quantity of chlorpyrifos compared to the cultivated sources. This may be due to the drift from nearby sources, such as cultivated agricultural fields. In another study reported that the contamination with dieldrin above the MRL established by the European Pharmacopoeia (50 ng/g) in Mikania laevigata, Maytenus ilicifoliaand Cordia verbenacea from an experimental field in Paulínia, SP, Brazil [8]. Sarkhail *et al*. [11] monitored the Levels of organophosphorus pesticides including parathion, malathion, diazinon and pirimiphos methyl in medicinal plants commonly consumed in Iran. The detected residues of diazinon and malathion were found in *Zataria*, *Matricaria chamomile*, Spearmint and Cumin Seed below the recommended MRLs.

Conclusion

The quality of the source materials used in the production of herbal medicines determines to a large extent the safety and efficacy of herbal remedies. In recent years, numerous analytical methods have been reported for determination of pesticide residues in medicinal plants and they are limited to selected compounds or groups such as OCs, OPs and SPs. Studies on validation of multiresidue analytical method can be used for monitoring pesticide residues in medicinal plants will be used for determination of pesticide levels in these samples. The medicinal plant samples should be monitored for contaminants regardless of whether they are cultivated or collected from the wild to determine the patterns of pesticide residue contamination in medicinal plants with sources of agricultural and industrial pollution which would strengthen international trade and safeguard the health of the consumers.

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