A REVIEW ON RECENT ANALYTICAL METHODS FOR DETECTION OF ADULTERANTS IN HERBAL MEDICINE

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Abstract: **The different analytical methods were used as NMR, TLC, HPLC, IR, LC-MS, capillary electrophoresis for the detection of adulterants like sibutramine, venlafaxine, obtusiloba, caffeine, sildenafil etc. in different herbal medicine. NMR method was found to be screening method for the detection, identification and quantitation of adulterants. TLC method was found to be newly developed method for separation and detection of complex ingredients such as sibutramine. HPLC method was found to be desirable method, because it minimizes sample preparation. HPLC system equipped with two-dimensional data analysis capability will provide a more define identification of adulterants. Capillary electrophoresis was found to be rapid and selective screening, identification, quantification of the adulterants. IR spectroscopy was found to be chemical pattern recognition to their origin and processing method for detection of adulterants. LC-MS method was found to be simultaneous precise and quantitative detection and measuring various adulterants. GC-MS method was found to be screening method for detection of adulterants and most frequent adulterants detected in this method.**

Keywords**: Herbal Medicine, Adulteration, NMR, TLC, HPLC, IR, Capillary Electrophoresis, Raman Spectroscopy, GC-MS.**

INTRODUCTION:

1. HERBAL MEDICINE:

(i) Definition:

- The art and practice of using herbs and herbal preparation to maintain health and to prevent, alleviate, or cure disease.
- A plant or plant part or an extract or mixture of these used in herbal medicine.

Figure. Herbal Medicine

(ii) Herbs used in Herbal Medicine:

- Raw Garlic
- Ginger
- Turmeric
- Ginseng
- Milk Thistle
- Feverfew
- St. John's Wort
- Ginkgo Biloba
- Saw Palmetto
- Aloe Vera

2. *ADULTERATION:*

- An adulterant is caused by the act of adulteration, a practice of secretly mixing a substance with another. Typical substances that are adulterated include but are not limited to food, cosmetics, pharmaceuticals, fuel, or other chemicals, that compromise the safety or effectiveness of the said substance.
- Adulteration is defined as the process by which the quality or the nature of a given substance is reduced through the addition of a foreign or an inferior substance and the removal of a vital element.
- It will not normally be present in any specification or declared substances due to accident or negligence rather than intent, and also for the introduction of unwanted substances after the product has been made.
- Adulteration, therefore, implies that the adulterant was introduced deliberately in the initial manufacturing process, or sometimes that it was present in the raw materials and should have been removed, but was not.[13,14]
- The adulteration and substitution of herbal drugs is the burning problem in herbal industry and it has caused a major effect in the commercial use of natural products.
- Adulteration in market samples is one of the greatest drawbacks in promotion of herbal products.
- Adulteration it is a practice of substituting the original crude drug partially or fully with other substances which is either free from or inferior in therapeutic and chemical properties or addition of low grade or spoiled drugs or entirely different drug similar to that of original drug substituted with an intention of enhancement of profits.
- An adulteration means a process of addition of impure, cheap and filthy substances to genuine drug in order to get more profits.
- The adulterants may not have pharmacological or therapeutic properties.
- Adulterants are the substance or poor-quality products added to food items for economic and technical benefits.

(i)TYPES OF ADULTERATION:

- Substitution with superficially similar inferior drugs
- Substitution with artificially manufactured substance
- Substitution with exhausted drug
- Substitution with synthetic chemicals to enhance natural character
- Presence of vegetative matter of same plant
- Harmful adulterants
- Adulteration of powders

➢ Substitution with Superficially Similar Inferior Drugs
The drug which morphological resemble to the authentic drug but inferior in chemical or therapeutic potential is used as adulterant.

➢ Substitution with Artificially Manufactured Substance
Artificially prepared drugs by providing the general form or appearance like original drugs are used as substituent of the original one.

➢ Substitution with Exhausted Drug
After extracting the chemical constituents the residue or exhausted form of drug is sale as original one. Due to this the plant material loses its medicinal properties. This practice is common in case of drugs containing volatile oils. This type of fraud is done for the enhancement of profit.

➢ Substitution with Synthetic Chemicals to Enhance Natural Character
Synthetically prepared drugs are added to the original one to enhance natural characters.

➢ Presence of Vegetative Matter of Same Plant
Along with the useful part other vegetative parts of same plant or other plant is added to the original one. It can be occur due to negligence or carelessness during collection of plants.

➢ Harmful Adulterants
Sometimes waste form of drug which may be harmful for health is added to authentic drug.

➢ Adulteration of Powders
This type of adulteration is commonly done in powder form of drug to decrease its cost by increasing weight.

(ii)THERE ARE TWO WAYS OF ADULTERATION:

- Direct or Intentional adulteration:
  It is mostly done by the suppliers for enhancement of profit. Addition of harmful or inferior drug decreases the safety value of drugs.
- Indirect or Unintentional adulteration:
  This type of adulteration occurs without any bad intention due to incorrect identification of drugs.

(iii)REASONS FOR ADULTERATION:

- Scarcity of drug
- Confusion in vernacular names
- Lack of knowledge about authentic source
- Similarity in morphology
- Unscientific collection
- High price of drug in the market
- Substitution

➢ Scarcity of drug:
Tremendous increase in population leads to the increase in demand of herbal raw material. The limited natural resources, over explosion and less cultivation of medicinal plants leads to the scarcity of medicinal plants.

➢ Confusion in vernacular names:
More than one plant having same synonyms and confusion in vernacular name will result into adulteration.

➢ Lack of knowledge about authentic source:
Drugs that are used extensively as medicinal agent in folk but do not have description in authenticated books are consider as AnuktaDravya. Due to lack of knowledge and authentic sources of such drugs result into adulteration.

➢ Similarity in Morphology:
Drugs which looks morphologically similar are commonly adulterated.

➢ Unscientific collection:
Raw material required for big pharmacy or drug retailer is generally collected by local and uneducated person from field and forest. These persons are not qualified botanist or taxonomist who can identify and authenticate correct species of herb. This careless collection usually admixed the plants.

➢ High price of the drug in the market:
Drugs having higher cost are commonly adulterated with relatively low cost drug for more profit. Ex. Stamens of Nagkesara is adulterated with stamens of Punnag and Surangi.

➢ Substitution:
Due to unavailability of particular drug another substitute having similar therapeutical properties can be used.

(iv)DISADVANTAGES OF ADULTRATION:

- Adulteration causes denaturation & degradation of product
- Adulteration may leads to deterioration of product
- Adulterants may completely destroy the active constituents
- May cause artificial scarcity of drug
- That leads to damage of dosage form
- Adulteration leads to altering of drug nature
- The adulterants may cause damage to patient
- Adulterants may cause death of patient
- They may cause un wanted side effects in patients
- They lead to increase price of product
- They cause to increase formulation price of dosage form
- Adulteration leads to damage of containers also

3. ANALYTICAL MATHODS USED IN ADULTERATION:

- Nuclear Magnetic Resonance (NMR)
- Thin Layer Chromatography (TLC)
- High Performance Liquid Chromatography (HPLC)
- Infrared Spectroscopy (IR)
- Capillary Elecrophoresis
- Liquid Chromatography – Mass Specroscopy (LC-MS)
- Raman Specroscopy
- Gas chromatography – Mass spectroscopy (GC-MS)

- **Nuclear Magnetic Resonance (NMR):**

The principle of nuclear magnetic resonance is based on the spins of atomic nuclei. The magnetic measurements depend upon the spin of unpaired electron whereas nuclear magnetic resonance measures magnetic effect caused by the spin of protons and neutrons.

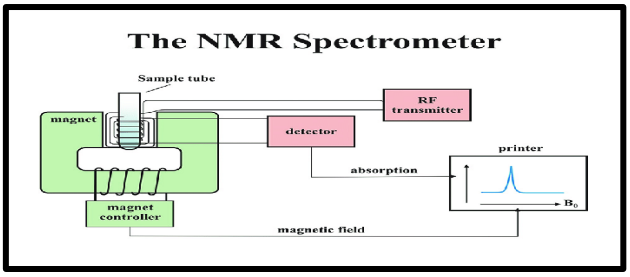

Figure. Schematic Diagram Of NMR

- **Thin Layer Chromatography (TLC):**

The separation principle of the TLC procedure is based on the given compound's relative affinity towards the mobile and the stationary phase. The process begins here by moving the mobile phase over the stationary phase's surface. During this movement, the higher affinity compounds gain less speed as compared to the lower affinity compounds. This results in their separation.

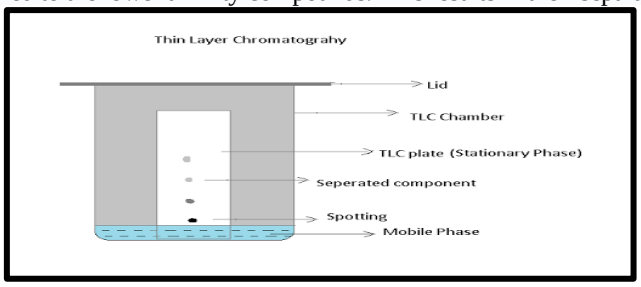

Figure.Schematic Diagram Of TLC

- **High Performance Liquid Chromatography (HPLC):**

The HPLC principle is based on the distribution of the component between a stationary phase (HPLC column) and a mobile phase (solvent). Depending on the chemical structure of the molecules they are retarded as passing the stationary phase. The intermolecular interactions among a sample's molecules and the packaging material determine their on-column period. Therefore, different components of a sample mixture are eluted at dissimilar retention times.

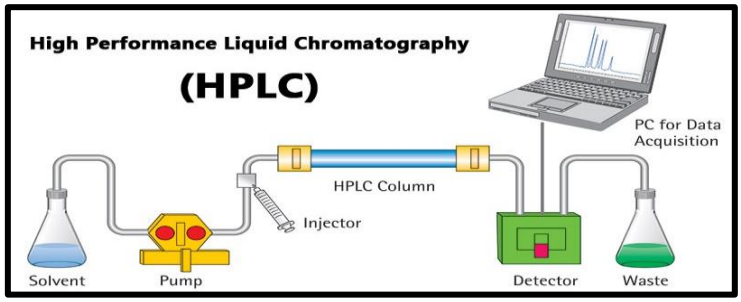

Figure. Schematic Diagram Of HPLC

- **Infrared (IR) Spectroscopy:**

The infrared spectroscopy is a vibrational energy level changes when radiation passes through the material.
The infrared spectroscopy is also known as vibrational spectroscopy. Infrared spectroscopy is based on the absorption or transmission of radiation.

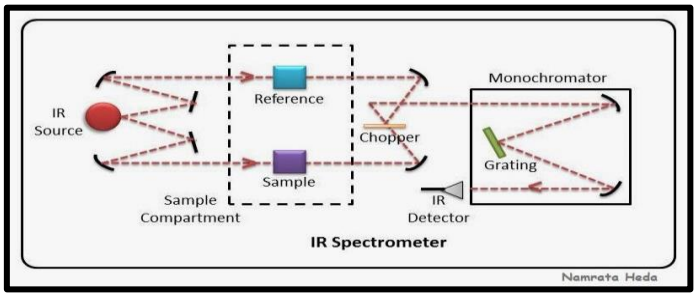

Figure. Schematic Diagram Of IR

- **Capillary Electrophoresis:**

Capillary electrophoresis is a method in which the sample ion moves through the influence of applied voltage. It pertains to the migration of charged ions in the electric field. In a given solution, the electric current flows between the electrodes and carried by ions.

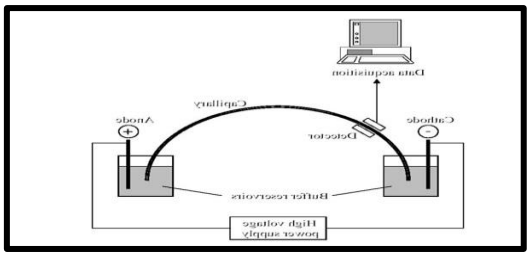

Figure. Schematic Diagram Of Capillary Electrophoresis

- **Liquid Chromatography -Mass Spectroscopy (LC-MS):**

The LC-MS technology involves use of an HPLC, wherein the individual components in a mixture are first separated followed by ionization and separation of the ions on the basis of their mass/charge ratio. The separated ions are then directed to a photo or electron multiplier tube detector, which identifies and quantifies each ion. The ion source is an important component in any MS analysis, as this basically aids in efficient generation of ions for analysis. To ionize intact molecules, the ion source could be APCI (Atmospheric Pressure Chemical Ionization), ESI (Electronspray Ionization), etc. to name a few popular ones. The choice of ion source also depends on the chemical nature of the analyte of interest i.e. polar or non-polar.

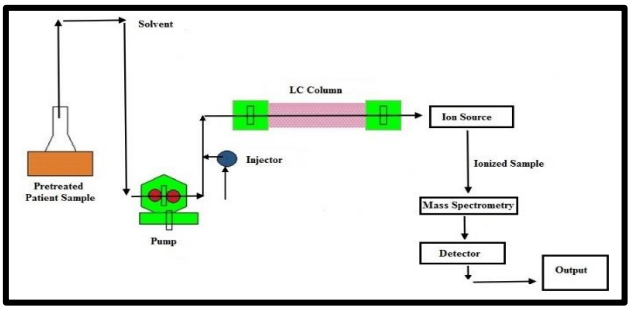

Figure. Schematic Diagram Of LC-MS

- **Raman Spectroscopy:**

When light interacts with molecules in a gas, liquid, or solid, the vast majority of the photons are dispersed or scattered at the same energy as the incident photons. This is described as elastic scattering, or Rayleigh scattering. A small number of these photons, approximately 1 photon in 10 million will scatter at a different frequency than the incident photon. This process is called inelastic scattering, or the Raman effect, named after Sir C.V. Raman who discovered this and was awarded the 1930 Nobel Prize in Physics for his work. Since that time, Raman has been utilized for a vast array of applications from medical diagnostics to material science and reaction analysis. Raman allows the user to collect the vibrational signature of a molecule, giving insight into how it is put together, as well as how it interacts with other molecules around it.

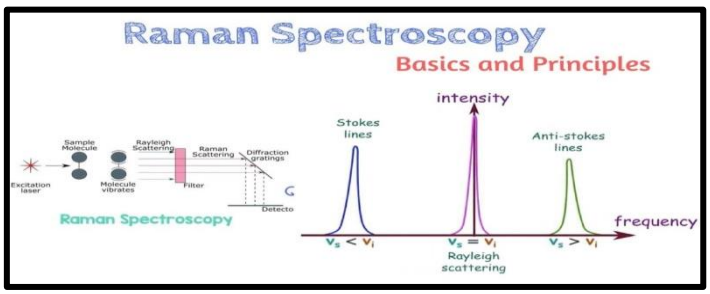

Figure. Raman Spectroscopy

- **Gas chromatography – Mass spectrometry (GC – MS):**

The GC works on the principle that a mixture will separate into individual substances when heated. The heated gases are carried through a column with an inert gas (such as helium). As the separated substances emerge from the column opening, they flow into the MS. Mass spectrometry identifies compounds by the mass of the analyte molecule. A library of known mass spectra, covering several thousand compounds, is stored on a computer. Mass spectrometry is considered the only definitive analytical detect Fig. 3.8 schematic diagram of GC-MS.

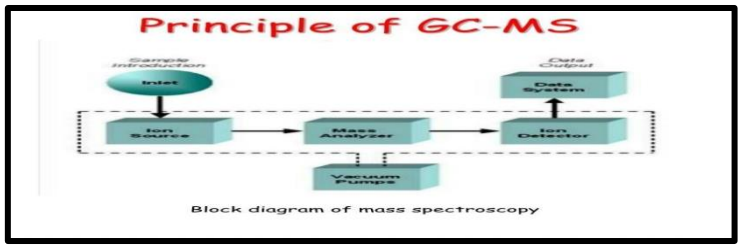

Figure. Schematic Diagram Of GC-MS

REVIEW OF LITERATURE

1.Syed A, Khan M, Khadim A (2021) were developed High Performance Liquid Chromatography (HPLC) methods for estimation of chemical adulterants such as A. obtusiloba (grows as weed) with Ziziphus jujuba in polyherbal formulation. A obtusiloba (grows as weed) with Ziziphus jujuba. The method was able to detect as low as 20% mixing of A. obtusiloba in medicinal herbal plant. HPLC system fitted with a binary RS pump, column thermostat and auto-sampler. Sample chromatography was performed on Macherey-Nagel Nucleodur C18 Gravity column.

2. Jiang Y, Cong S, Song G (2021) were developed Raman Specroscopy methods for estimation of chemical adulterants such as dye adulterants in Chinese herbal medicine. 80% and 120% and are indicative of its particular potential as a rapid and non destructive analytical method for monitoring Sudan dye adulterants in herbal medicine. Sudan Red 3 (SR3) adulterant even at an extremely low concentration of 0.3 mg/kg in various herbal medicines. indicating an acceptable detection limit that meets the safety limits set by the European Union (0.5 mg/kg).

3.Salahshour B, Sadeghi S, Nazari H (2020) were developed High Performance Liquid Chromatography with Diode Array Detector (HPLC -DAD) and Gas Chromatography – Mass Spectrometry (GC – MS) techniques for estimation of chemical adulterants such as Caffeine , trimethoxyamphetamine , and vitamin E in herbal weight loss product. The HPLC analysis was isocratically conducted on a C-18 column using a C-18 guard column. The GC column was HP-5 MS. Mass analyzer was connected to the column. Caffeine , trimethoxyamphetamine , and vitamin E was detected respectively: 21.8% , 6.25% of the samples as the most common undeclared active pharmaceutical adulterant.

4. Guo C, Gonga L, Wanga W (2020) were developed liquid chromatography -mass spectrometry(LC -MS) methods for estimation of chemical adulterants such as theophylline, prednisone acetate, chlorphenamine, dioxopromethazine in herbal medicine. . The intra and inter day accuracies were in the range of 92.4 to 108.3%, while the intra and inter day precision ranged from 2.6% to 8.7%. The result shows that the retention times (RTs) range from 1.44 min to 7.71 min . The detected antitussive adulterants include target adulterants such as theophylline, sulfamethoxazole, prednisone acetate, chlorphenamine, pentoxyverine and non-targeted adulterants such as trimethoprim, dioxopromethazine, aspirin, diclofenac and cephalexin, with levels in the range of 0.271 ~ 135.21 mg/g.

5. Ghaleh V, Moradi M, soltaninejad K (2019) were developed high performance liquid chromatography (HPLC) and gas chromatography mass spectrometery (GCMS) methods for estimation of pharmaceutical adulterants as . Diphenoxylate, tramadol methadone in herbal Medicinal Products Used in the Treatment of Opioid Addiction. HPLC system equipped with diode array detector (DAD) was used to analyze sample using C-18 column with a smart 1000 pump. Gas chromatography equipped with split/splitless injector was used. Diphenoxylate , tramadol , and methadone respectively concentration is 39.3% , 26.2% , and 13.2%.

6. Fard H, Akhgari M (2018) were developed high performance liquid chromatography (HPLC) and gas chromatography/mass spectrometry (GC/MS) methods for estimation of pharmacetical adulterants such as sildenafil, tramadol and diazepam in herbal sexual enhancer drugs. HPLC system equipped with diode array detector (DAD) was used to analyze sample using C-18 column with a smart 1000 pump. Gas chromatography equipped with split/splitless injector was used. The column of the GCwas HP5-MS model capillary column. Sildenafil contain 28% in herbal sexual enhancer drugs.

7.Dastjerdi A, Akhgari M, Kamali A (2018) were developed Gas chromatography / Mass spectrometry (GC /MS) methods for estimation of chemical adulterants such as tramadol, caffeine, fluoxetine, rizatriptan, venlafaxine and methadone in herbal supplements advised as weight loss drugs. An Agilent model A gas chromatograph equipped with split/splitless injector was used. The column was a HP5-MS capillary column. The capillary column was connected to a mass analyser . 72% were found to be adulterated with tramadol, caffeine, fluoxetine, rizatriptan, venlafaxine and methadone. Tramadol 21.3% , Caffeine 21.3%, Rizatriptan 11.5%, Fluoxetine 8.2%, Venlafaxine 6.6% , Methadone 1.6, %Ritodrine 1.6 %.

8.Mateescu C, Popescu A, Radu G (2017) were developed Gas chromatography / Mass spectroscopy (GC /MS) methods for estimation of chemical adulterants such as sildenafil , tadalafil and phenolphthalein in herbal Food Supplements. About 22% of herbal food supplements with sexual enhancement claims analyzed by spectroscopic methods proved with active pharmaceutical

compounds such as: sildenafil and tadalafil and phenolphthalein. The occurence of phenolphthalein could be the reason for the non-relevant results obtained by FTIR method.

9.Ching C, Chen S, Chih H (2017) were developed High Performance Liquid Chromatography (HPLC) methods for estimation of proprietary Chinese medicines adulterants such as anti inflammatory , anoretics , corticosteroids , diuretics , laxatives , oral antidiabetic , erectile dysfunction in Health products. The six most common categories of adulterants detected were nonsteroidal anti-inflammatory drugs (17.7%), anorectics (15.3%), corticosteroids (13.8%), diuretics and laxatives (11.4%), oral antidiabetic agents (10.0%) and erectile dysfunction drugs (6.0%).

10.Hachema R, Assemat G, Martins N (2016) were developed Nuclear Magnetic Resonance (NMR) methods for estimation of chemical adulterants such as Sibutramine and Phenolphthalein in Herbal food supplements marketed for weight loss. The 1H NMR experiments were performed on a Bruker Avance 500 spectrometer . The Sibutramine and Phenolphthalein result was found to be 46% and 39% respectively.

11. Woźniak K, Georgiev M, Erdogan I (2016) were developed Nuclear Magnetic Resonance (NMR) methods for estimation of chemical adulterants such as sildenafil in herbal sexual enhancers and slimmers. In 4% of the tested products undeclared sildenafil was detected, while another 54% contained its analogues such as acetildenafil, hydroxyacetildenahydroxyhomosildenafil, and piperidenafil. H-NMR was used as a powerful technique for detection, identification and quantification of adulterants .PDE 5 inhibitors are detected in health supplements used for sexual performance enhancement such as i.e. dapoxentine , which is reported to be a selective serotonin re-uptake inhibitor under investigation for the treatment of premature ejaculation.

12.Viana C, Zemolin G, Muller L (2015) were developed High Performance Liquid Chromatography (HPLC) methods for estimation of chemical adulterants such as , caffeine, p-synephrine, hordenine, octopamine, tyramine, ephedrine, and salicin in food supplements for weight loss and physical fitness. . The validated HPLC DAD (Diode array detection) method was applied to the study of food supplements. Caffeine was found to be present 52%. p-synephrine was present in 6.5% and ephedrine only in 2.2%. caffeine was found to be the stimulant more frequently used in the supplements.

13. Cavalcante N, Honorato R, Pimente M (2015) were developed Nearinfrared(NIR) spectroscopy for estimation of chemical adulterants such as sibutramine in herbal medicine in weight loss treatment. Spectra were obtained in the range of 14,000–4000 per cm. Using PLS-DA, a correct classification of 100% was achieved for the external validation set. In the quantitative approach, the root mean squares error of prediction (RMSEP), for both PLS and MLR models, was 0.2%w/w. The results prove the potential of NIR spectroscopy and multivariate calibration in quantifying sibutramine in adulterated herbal medicines samples.

14.Khazana M, Hedayati M, Askari S (2013) were developed liquid chromatography–tandem mass spectrometry (LC–MS/MS) methods for estimation of chemical adulterants such as sibutramine and ephedrine in herbal medicine for weight loss with thyroid hormone and PCP. The contents of the samples were also analyzed for thyroxine (T4) and thiiodothyroinine (T3) by radioimmunoassay (RIA) . The intra-assay coefficients of variation for both tests were less than 7%. The sensitivity of assay kits was 0.3nmol/l and 7nmol/l for T3 and T4 respectively. Both the immunochro+matographic and radioimmunoassay.

15.Moreiraa A, Mottab M, Molinb T (2013) were developed capillary zone elecrophoresis methods for estimation of diuretic and laxatives adulterants such as furosemide, hydrochlorothiazide, chlorthalidone and amiloride (diuretics), phenolphthalein (laxative), amfepramone (anorexic) and fluoxetine and paroxetine (antidepressants) by capillary zone electrophoresis with capacitively coupled contactless conductivity detection in herbal formulation for weight loss. The method allowed the drugs to be determined in the formulations at concentrations higher than 5.1 mg/kg for amiloride, 7.7 mg/kg for chlorthalidone, 6.8 mg/kg for hydrochlorothiazide, 10.7 mg/kg for furosemide, 8.4 mg/kg for phenolphthalein, 11.0 mg/kg for fluoxetine, 9.4 mg/kg for paroxetine and 11.0 mg/kg for amfepramone.

16. De Carvalhoab L, Cohencd P, Silvaae C, (2012) were developed capillary electrophoretic (CE) methods for estimation of chemical adulterants such as amfepramone , fenproporex , sibutramine , fluoxetine , bupropion , sertraline , paroxentine and flurazepam in herbal weight loss product. CE measurements were performed using a CE system equipped with a capacitively coupled contactless conductively detector (CD). The optimized method had the following results for the main analytical validation parameters for amfepramone , fenproporex , sibutramine , fluoxetine respectively : 205.0, 235.0, 265.0 and 205.0 mg kg-1 for limits of detection (LOD) ; 675.0 , 780.0, 875.0 and 690.0 mg kg-1 for limits ofquantification (LOQ); 9.8 %, 8.9% , 6.1% and 8.5% for precision (RSD); and 95.4%, 112.4%, 108.9% for accuracy.

17. Vaysse J , Balayssac S , Gilard V (2010) were developed Nuclear Magnetic Resonance NMR methods for estimation of chemical adulterants such as sibutramine , phenolphthalein , synephrine , methylsynephrine , caffein in dietary supplements and herbal weight loss product. The concentrations of adulterant compounds were measured by comparing the expanded areas of their respective NMR signals with that of the internal standard for quantification TSP. NMR spectrum also helped to substantiate compound identification.

18.Wang J, Chen B, Yao S (2008) were developed High Performance Liquid Chromatography (HPLC) methods for estimation of chemical adulterants such as fenfluramine, phenolphthalein, N-di-desmethyl sibutramine, N-mono-desmethyl sibutramine, sibutramine, orlistat and sildenafil in Herbal weight reducing dietary supplements. The retention times of fenfluramine, phenolphthalein, N-di-desmethyl sibutramine, N-mono-desmethyl sibutramine, sibutramine, orlistat and sildenafil were 4.45, 5.14, 7.96, 8.68, 13.44, 19.64 and 6.20 min, respectively.

19.Cianchino V, Acosta G, Ortega C (2008) were developed capillary elecrophoresis methods for estimation of chemical adulterants such as Ephedrine, norephedrine, caffeine and furosemide in herbal medicine and dietary supplements for weight control. The CE system consist of Diode array detector and data handling system. Detection was performed at 208 and 265nm. Ephedrine, norephedrine, caffeine and furosemide were found in sample in concentrations of 0.45 ± 0.03 mg g1 , 0.33 ± 0.02 mg g1 , 1.09 ± 0.41 mg g1 and 0.80 ± 0.17 mg g1.

20.Liang Q, Qu J, Luo G (2006) were developed High Performance Liquid Chromatography (HPLC) methods for estimation of chemical adulterants such as sildenafil and famotidine in herbal medicine and dietary supplements. The sildenafil and famotidine

lower limits of detection of these compounds ranged from 0.05 to 1.5 ng/ml. The necessity of the use of a short C18 column. column was capable of improving peak shapes, stabilizing signal intensities and narrowing peak widths of some analytes comparing with flow injection analysis (FIA).
21.Huang W, Wen K, Hsiao M (1997) were developed Thin layer chromatography (TLC) methods for estimation of chemical adulterants such as Phenylbutazone, prednisolone, and corticosteroids inrheumatoid or an anti-inflammatory. The concentration of Phenylbutazone, prednisolone, and corticosteroid are respectively 27.7%, 25.3%, and 22.3%. one third of the adulterated samples (34.5%) contained caffeine, at least a quarter contained acetaminophen (27.0%) or indomethacin (24.6%), a fifth (20.6%) contained hydnochiorothiazide and more than one tenth contained prednisolone (14.8%), chlorzoxazone (14.1%), or ethoxybenzamide (10.7%).

CONCLUSION

From the review of various literature, it was concluded that different analytical methods were used as NMR, TLC, HPLC, IR, LC-MS, capillary electrophoresis for the detection of adulterants like sibutramine, venlafaxine, obtusiloba, caffeine, sildenafil etc. in different herbal medicine. It has various application in pharmaceutical industry and research laboratory.

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