Summary and Conclusion

In the past decade, there has been renewed attention and interest in the use of traditional medicine (Ayurveda, Yoga, Naturopathy, Unani, Siddha and Homeopathy) in India and globally. It is estimated that 65% of the population in rural India use medicinal plants to meet primary health care needs. So it is the cardinal responsibility of the regulatory authorities to ensure that the consumers get the medication, with guarantee which includes purity, safety, potency and efficacy. Modern medicine which is continuously undergoing metabolic changes and improvements in the standard of purity, safety and efficacy. Thus maintaining the quality of Herbal medication becomes the sole responsibility of the manufacturer and scientists working in this field.

Plant material and herbal remedies derived from them represent substantial portion of global market and in this respect internationally recognized guidelines for their quality assessment and quality control are necessary. The traditional medicine (Ayurveda, Yoga, Naturopathy, Unani, Siddha and Homeopathy) have been given due recognition by the regulatory bodies in the recent past. Recently, many international authorities and agencies including the world health organization, European Agencies for the evaluation of medicinal product and European Scientific Co-operation of phyto-medicine, U.S. Agencies for Health Care Policy and Research, European Pharmacopoeia Commission, department of Indian System of Medicine have started creating a new mechanism to induce quality control and standardization of traditional medicine. WHO has emphasized the need to ensure quality control of medicinal plant products by using modern technique and by applying suitable parameters and standards.

Patent proprietary Ayurvedic medicines are sold over the counter in pharmacies. These products appear to represent a major share of branded traditional medicine in India. Nevertheless systems like Ayurveda still need to gain an empirical support of modern medical sciences to make them credible and acceptable for all, in this regard.
it is a need to develop the modern dosage form like Tablet, Mouth Dissolving Tablets and Capsules of traditional dosage form (vati, gutika, churna or safoof etc.) with respect to increase the stability, dose accuracy, production rate, quality of packaging material, elegance of design, overall aesthetic appeal and so on. Some innovative research efforts are required to define the advantages of standardization and development of modern dosage form to make the herbal drug acceptable globally. The present study is an approach to develop quality control parameters and development of modern dosage form (Capsule) of identified formulations viz., Balacaturbhadrika churna (Ayurvedic), Shingyadi churna (Ayurvedic), Thirikadu choornam (Siddha) and Safoof-E-Sana (Unani) which are official in their respective formularies.

5.1 Standardization of Balacaturbhadrika churna

Balacaturbhadrika churna is a fine powder form, which is widely used in Diarrhoea, Fever, Cough and Asthma at dose of 500 mg to 1 gm/day. It is composed of *Cyperus rotundus* (musta), *Piper longum* (pippali), *Aconitum heterophy* (ativisa) and *Pistacia integerrima* (sringi). All the ingredients are firstly powdered separately and mixed together. All the plant raw materials were purchased from the local market of Raipur, C.G. and identified morphologically and microscopically and compared with standard pharmacopoeial monograph. All the reagents and solvents used were of analytical grade. The sample of crude drug was also authenticated by University Institute of Pharmacy, Pandit Ravishankar Shukla University, Raipur. The ash values, extractive values with various reagents were determined as per the WHO guidelines.

Three batches of Balacaturbhadrika churna designated as BC-I, BC-II and BC-III, were prepared in laboratory using method described in Ayurvedic Formulary of India. Evaluation of organoleptic characters of raw materials Ghana (musta), Krsna (pippali), Aruna (ativisa) and Sringi (karkatasringi) was performed and characters are recorded. Laboratory batches of Balacaturbhadrika churna (BC-I, BC-II and BC-III) and one marketed preparations were also evaluated for organoleptic characters. The results for the marketed formulation (MF) and Laboratory formulations (LF) are found comparable.
The moisture content of formulation was within acceptable range (<8%) thus implying that the formulation can be stored for a long period and would not easily be attacked by microbes. Physical properties namely tapped density, bulk density, angle of repose, hausner ratio and carr’s index were calculated for Lab formulation, marketed formulation and its raw materials. The value of angle of repose for raw materials *Cyperus rotundus*, *Piper longum*, *Aconitum heterophy*, *Pistacia integerrima*, lab formulation (BC-I) and marketed formulation were 28.62, 31.28, 29.86, 24.34, 27.36, and 27.45 respectively which shows good flow properties of prepared lab formulation. The flow properties of lab (BC-I) and marketed formulations were also confirmed by Hausner’s ratio and Carr’s index; it was found 1.25, 20, and 1.19, 16 respectively and indicates good flow characteristics.

Results of the phytochemical screening of the raw materials, lab formulation and marketed formulation of Balacaturbhadrika churna were concluded. One notable difference as a result of the method of extraction is the alkaloids in *Piper longum* and *Pistacia integerrima* are more soluble in ethanol than aqueous extract. We were performed more than one test for the detection of a chemical group such as the alkaloids, no differences in the results were observed for the different tests. Out of the nine phytochemical groups investigated, seven namely carbohydrate, glycosides, tannins, flavonoids, fixed oil and proteins were detected in the ethanolic extract of lab and marketed formulations however the aqueous extracts of both formulations shows the presence of saponins with previously stated seven phytochemical groups. Steroids were absent in all the ingredients and formulations for both methods of extraction.

Total ash value of *Cyperus rotundus*, *Piper longum*, *Aconitum heterophy*, *Pistacia integerrima*, lab formulation (BC-I) and marketed formulation were found 7.346±0.346, 5.032±0.624, 2.981±0.243, 4.621±0.334, 8.148±0.337 and 19.633±0.552 respectively. The value of total ash in marketed formulation is comparatively high in comparison to lab formulation may be because of the higher amounts of inorganic components present in marketed formulation.

Alcohol-soluble and water soluble extractive values of ingredients and formulations were performed as per WHO guidelines. Higher ethanol-soluble extractive value
Summary and Conclusion

(39.294±2.226 and 30.662±0.472 for lab and marketed formulations respectively) implies that ethanol is a better solvent of extraction for the formulation than water. Arsenic and heavy metals are below the specified limit in all ingredients, lab and marketed formulations. Tests were also performed for specific pathogen as per the WHO (1998) guidelines. E. coli, Salmonella species and S. aureus were found absent. This ensures the level of safety of formulation.

- **Spectrophotometric analysis**

The spectrophotometric determination of formulations was carried out through UV spectrophotometer at 342.5 nm for piperine. The absorbance characteristics show that piperine follow Beer Lambert’s law within the concentration range 2-10 µg/ml at the $\lambda$-max of 342.5 nm. The estimation of piperine content of the Balacaturbhadrika churna and powder of *Piper longum* (Pippali) was carried out separately. The concentration of piperine content in raw material was found to be 1.852 ± 0.241 % w/w in *Piper longum*. The content of piperine in different batches of Balacaturbhadrika churna was found to be 0.435 ± 0.030, 0.424 ± 0.001, 0.430 ± 0.004 and 0.346 ± 0.002 % w/w respectively for lab formulation (BC-I, BC-II, BC-III) and marketed formulation (MF). Recovery studies are indicative of reproducibility of method. Hence the present method is simple, sensitive, precise and accurate and can be adopted for routine quality control of Balacaturbhadrika churna.

- **HPLC fingerprinting method**

The study is an attempt to develop the fingerprint method for Balacaturbhadrika churna by simple high-performance liquid chromatography (HPLC) determination using piperine as a standard, which are important and major content in formulation. RP- HPLC methods for simultaneous determination of piperine have been developed. A C 18 LUNA (5 micron 25 cm×4 mm) column from Phenomenex in binary gradient mode with mobile phase methanol at flow rate is 1.0ml/min used and effluent was monitored at 343 nm. Validation of the method was done with a view to demonstrate its selectivity, linearity, precision and accuracy. The content of piperine was found to be 1.852 ± 0.124, 0.435 ± 0.025, 0.424 ± 0.241, 0.430 ± 0.262 and 0.346
± 0.762 % w/w respectively for *Piper longum*, lab formulation (BC-I, BC-II, BC-III) and marketed formulation (MF).

- **HPTLC fingerprinting method**

HPTLC fingerprint method for Balacaturbhadrika churna using piperine as a standard is developed. The piperine is an important content in the formulation and all of its herbal raw ingredients. The method was validated for linearity, accuracy, limit of detection, limit of quantification, inter-day and intra-day assay precision, repeatability of measurement, and repeatability of sample application. The content of piperine was found to be 1.92 ± 0.08, 0.442 ± 0.005, 0.431 ± 0.023, 0.430 ± 0.081 and 0.362 ± 0.242 % w/w respectively for *Piper longum*, lab formulation (BC-I, BC-II, BC-III) and marketed formulation (MF).

The statistical analysis proved that the method is reproducible and efficient for the analysis of piperine in formulations. These findings can be used as routine chromatographic fingerprinting method for the standardization of the herbal raw materials as well as the finished formulation of Balacaturbhadrika churna.

- **Stability studies**

During accelerated stability studies as per WHO (1998) physicochemical parameters viz. colour, odour, taste, moisture content, and piperine content are studied. The result of study reveals that there are no or little observable changes in the parameters during a time period of 6 months. It indicates that the formulations are stable under the different stability studies parameters.

5.2 **Standardization of Shringyadi churna**

Shringyadi churna is an Ayurvedic alternative medicine which is used in diarrhea, fever, cough and asthma. It composed of dried powders of *Pistacia integerrima* (karkatasringi), *Piper longum* (pippali) and *Aconitum palmatum* (ativisa).

All the ingredients are firstly powdered separately and mixed together. All the plant raw materials were purchased from the local market of Raipur, C.G. and identified morphologically and microscopically and compared with standard pharmacopoeial...
monograph. The sample of crude drug was also authenticated by University Institute of Pharmacy, Pandit Ravishankar Shukla University, Raipur. All the reagents and solvents used were of analytical grade. The ash values, extractive values with various reagents and were determined as per the WHO guidelines. Three batches of Shringyadi churna designated as SC-I, SC-II and SC-III, were prepared in laboratory using method described in Ayurvedic Formulary of India. Evaluation of organoleptic characters of raw materials *Pistacia integerrima* (karkatasringi), *Piper longum* (pippali) and *Aconitum palatum* (ativisa) were performed and characters are recorded.

Laboratory batches of Shringyadi churna (SC-I, SC-II and SC-III) and one marketed preparations were also evaluated for organoleptic characters. The results for the marketed formulations M I and Laboratory formulation are found comparable. The moisture content of formulation was within acceptable range that is 2.24±0.242 and 2.32±0.282 for lab and marketed formulations respectively thus implying that the formulation can be stored for a long period and would not easily be attacked by microbes. Physical properties namely tapped density, bulk density, angle of repose, hausner ratio and carr’s index were calculated for Lab formulation, marketed formulation and its raw materials. The value of angle of repose for raw materials *Pistacia integerrima* *Piper longum*, *Aconitum palatum*, lab formulation (SC-I) and marketed formulation were 24.34, 31.28, 29.86, 26.86 and 25.42 respectively which shows good flow properties of prepared lab formulation. The flow properties of lab (SC-I) and marketed formulations were also confirmed by Hausner’s ratio and Carr’s index; it was found 1.25, 20, and 1.23, 19 respectively and indicates good flow characteristics.

Seven phytochemical groups namely carbohydrate, glycosides, tannins, flavonoids, fixed oil and proteins were detected in the ethanolic extract of lab and marketed formulations however the aqueous extracts of both formulations shows the presence of saponins with previously stated seven phytochemical groups. Steroids were absent in all the ingredients and formulations for both methods of extraction. Results also
Summary and Conclusion

confirm that both formulations are more soluble in ethanol than water. It depicts that constituents present in formulations are more soluble in ethanol.

Total ash value of *Pistacia integerrima, Piper longum, Aconitum palmatum*, lab formulation and marketed formulation were 5.032 ± 0.624, 2.981 ±0.243, 4.621 ±0.334, 7.224 ± 0.247 and 19.633 ± 0.552 respectively. The value of total ash in marketed formulation is comparatively high in comparison to lab formulation may be because of the higher amounts of inorganic components present in marketed formulation. Acid-insoluble ash value of lab (SC-I) and marketed formulation were found 3.446 ± 0.268 and 5.041 ± 0.368 respectively shows that a small amount of the inorganic component is insoluble in acid it indicates adulteration of raw ingredients by substance like silica, rice husk is very less in both formulation. Low acid-insoluble ash value may also affect amount of the component absorbed in the gastrointestinal canal when taken orally.

Alcohol-soluble extractive values were found 38.486±1.842 and 31.824±0.251 for lab and marketed formulation respectively which is higher than water soluble extractive value of both formulations. Higher ethanol-soluble extractive value implies that ethanol is a better solvent of extraction for the formulation than water.

**Spectrophotometric analysis**

The spectrophotometric determination of formulations was carried out through UV spectrophotometer at 342.5 nm for piperine. The absorbance characteristics show that piperine follow Beer Lambert’s law within the concentration range 2-10 µg/ml at the λ-max of 342.5 nm. The estimation of piperine content of the Shringyadi churna and powder of *Piper longum* (Pippali) was carried out separately. The concentration of piperine content in raw material was found to be 1.852 ± 0.241 w/w in *Piper longum*. The content of piperine in different batches of Shringyadi churna was found to be 0.605 ± 0. 001 %, 0.599 ± 0.127 %, 0.602 ± 0.008 % and 0.535 ± 0.015 % w/w respectively for lab formulation (SC-I, SC-II, SC-III) and marketed formulation (MF) respectively. Recovery studies are indicative of reproducibility of method. Hence the
Summary and Conclusion

The present method is simple, sensitive, precise and accurate and can be adopted for routine quality control of Shringyadi churna.

- **HPLC fingerprinting method**

  The study is an attempt to develop the fingerprint method for Shringyadi churna by simple high-performance liquid chromatography (HPLC) determination using piperine as a standard, which are important and major content in formulation. RP-HPLC methods for simultaneous determination of piperine have been developed. A C 18 LUNA (5 micron 25 cm×4.6 mm) column from Phenomenex in binary gradient mode with mobile phase methanol at flow rate is 1.0ml/min used and effluent was monitored at 342.5 nm. Validation of the method was done with a view to demonstrate its selectivity, linearity, precision and accuracy. The content of piperine was found to be 1.852 ± 0.001, 0.605 ± 0.012, 0.599 ± 0.119, 0.602 ± 0.106 and 0.535 ± 0.549 % w/w respectively for *piper longum*, lab formulation (SC-I, SC-II, SC-III) and marketed formulation (MF) respectively.

- **HPTLC fingerprinting method**

  HPTLC fingerprint method for Shringyadi churna using piperine as a standard is developed. The piperine is an important content in the formulation and all of its herbal raw ingredients. The method was validated for linearity, accuracy, limit of detection, limit of quantification, inter-day and intra-day assay precision, repeatability of measurement, and repeatability of sample application. The content of piperine in different batches of Shringyadi churna was found to be 1.920 ± 0.082, 0.624 ± 0.005, 0.618 ± 0.046, 0.614 ± 0.032 and 0.569 ± 0.225 % w/w respectively for *piper longum*, lab formulation (SC-I, SC-II, SC-III) and marketed formulation (MF) respectively.

  The statistical analysis proved that the method is reproducible and efficient for the analysis of piperine in formulations. These findings can be used as routine chromatographic fingerprinting method for the standardization of the herbal raw materials as well as the finished formulation of Shringyadi churna.
• Stability studies

During accelerated stability studies physicochemical parameters as per WHO (1998) viz. colour, odour, taste, moisture content, and piperine content are studied. The result of study reveals that there are no or little observable changes in the parameters during a time period of 6 months. It indicates that the formulations are stable under the different stability studies parameters.

5.3 Thirikadu choornam

Thirikadu choornam is well known Siddha Formulation, comprised of the fruits of two medicinal important plants *Piper longum* (Pippali), *Piper nigrum* (Marica) and rhizomes of *Zingiber officinale* (Saunth). Thirikadu choornam is a digestive tonic for the assimilation of other foods in the body. It is also used as a rejuvenator and stimulant. Thirikadu choornam plays an essential role in the treatment of a wide variety of conditions.

Thirikadu choornam, three batch namely TC-I, TC-II, TC-III, were prepared in laboratory according to method described in Siddha Pharmacopoeia.

Evaluation of organoleptic characters of powdered raw material (*Piper longum*, *Piper nigrum*, and *Zingiber officinale*) was performed and characters are recorded. Laboratory batches of Thirikadu choornam (TC-I, TC-II and TC-III) and one marketed preparations were also evaluated for organoleptic characters. The results for the marketed formulation and Laboratory formulation were found comparable.

The value of angle of repose for raw materials *Piper longum* (Pippali), *Piper nigrum* (Marica), *Zingiber officinale* (Saunth), lab formulation (TC-I) and marketed formulation were 25.34, 25.43, 26.68, 26.61 (TC-I), 23.54, and 26.47 respectively which shows good flow properties of prepared lab formulation. The flow properties of lab (TC-I) and marketed formulations were also confirmed by Hausner’s ratio and Carr’s index; it was found 1.20, 16.95, and 1.29, 22.41 respectively and indicates good flow characteristics.

The amount of moisture in the crude drugs should be minimized in order to prevent decomposition of either due to chemical changes or due to microbial contamination.
Summary and Conclusion

The percent moisture content for TC-I, TC-II and TC-III are 2.82±0.124, 2.93±0.442 and 2.76±0.125, while it is 2.93±0.323 for MF. The moisture content of formulation was within acceptable range (<8%) thus implying that the formulation can be stored for a long period and would not easily be attacked by microbes. The percent of foreign matter was found to be 1.29±0.084, 1.08±0.129 and 1.46±0.125 for PL (Piper longum), PN (Piper nigrum), ZO (Zingiber officinalis) respectively. Laboratory formulations of Thirikadu choornam were prepared after removal of foreign matter. In examination no poisonous, dangerous and harmful foreign matter or residue was found.

Total ash value of PL (Piper longum), PN (Piper nigrum), ZO (Zingiber officinalis), lab formulation (TC-I) and marketed formulation were 3.281 ± 0.548, 4.469 ± 0.276, 5.237 ± 0.342, 4.232 ± 0.321 and 5.235 ± 0.732 respectively. The value of total ash in marketed formulation is comparatively high in comparison to lab formulation may be because of the higher amounts of inorganic components present in marketed formulation. Acid-insoluble ash value of prepared lab formulations (TC-I) and marketed formulation were 0.681 ± 0.043 and 0.636 ± 0.056 respectively shows that a small amount of the inorganic component is insoluble in acid it indicates adulteration of raw ingredients by substance like silica, rice husk is very less in both formulation. Low acid-insoluble ash value may also affect amount of the component absorbed in the gastrointestinal canal when taken orally.

Alcohol-soluble and water soluble extractive values of lab and marketed formulation were 39.478±1.546 and 31.014±0.321 respectively which is higher than water soluble extractive value of both formulations. Higher ethanol-soluble extractive value implies that ethanol is a better solvent of extraction for the formulation than water.

The presence of different constituents in the Thirikadu choornam and its raw materials is detected by their phytochemical analysis. The formulations are found to contain alkaloids, carbohydrates, volatile oil, resin, saponins and proteins. The same constituents are present in marketed preparations.

- Spectrophotometric analysis
Summary and Conclusion

The spectrophotometric determination of formulations was carried out through UV spectrophotometer at 342.5 nm for piperine. The absorbance characteristics show that piperine follow Beer Lambert’s law within the concentration range 2-10 µg/ml at the λ-max of 342.5 nm. The estimation of piperine content of the Thirikadu choornam *Piper longum* (Pippali) and *Piper nigrum* (Marica) was carried out separately. The concentration of piperine content in raw material was found to be 1.852 ± 0.241 w/w in *Piper longum* and 3.685 ± 0.164. The content of piperine in different batches of Thirikadu choornam was found to be 1.829 ± 0.011, 1.823 ± 0.145, 1.826 ± 0.123 and 1.635 ± 0.156 % w/w respectively for lab formulation (TC-I, TC-II and TC-III) and marketed formulation (MF) respectively. Recovery studies are indicative of reproducibility of method. Hence the present method is simple, sensitive, precise and accurate and can be adopted for routine quality control of Thirikadu choornam.

- **HPLC fingerprinting method**

With a view to develop the fingerprint method for Thirikadu choornam, simple high-performance liquid chromatography (HPLC) determination using piperine as a standard was performed. RP- HPLC methods for determination of Piperine from the fruits of Pippali, Marica and Thirikadu choornam have been developed. A C 18 LUNA (5 micron 25 cm×4.6 mm) column from Phenomenex in binary gradient mode with mobile phase methanol at flow rate is 1.0ml/min used and effluent was monitored at 342.5 nm. Validation of the method was done with a view to demonstrate its selectivity, linearity, precision and accuracy. The piperine is the chief constituent of the Thirikadu choornam and two of its component of fruits of *Piper longum* (Pippali), *Piper nigrum* (Marica). The concentration of piperine present in raw materials is found to be 3.685 ± 0.164 w/w in *Piper nigrum* and 1.852 ± 0.001 w/w in *Piper longum* respectively and in three identical laboratory batch of Thirikadu choornam name TC-I, TC-II and TC-III and marketed formulation were 1.841 ± 0.005, 1.837 ± 0.009, 1.832 ± 0.111 and 1.645 ± 0.741 % w/w respectively. The HPLC method developed for the estimation of piperine was validated by statistical analysis and recovery studies.
Summary and Conclusion

- **HPTLC fingerprinting method**

  To develop the solvent system samples were run in different solvent. Better results are obtained with mobile phase consisting toluene: ethyl acetate (70:30v/v). On the basis of TLC profile HPTLC study is performed. HPTLC fingerprint method is developed for Thirikadu choornam using piperine as a standard, which is an important and major content of formulation. HPTLC methods for determination of piperine from the Thirikadu choornam along with its raw materials have been developed. The method was validated for linearity, accuracy, limit of detection, limit of quantification, inter-day and intra-day assay precision, repeatability of measurement, and repeatability of sample application. The concentration of piperine present in raw materials is found to be 3.699 ± 0.064 w/w in *Piper nigrum* and 1.889 ± 0.011 w/w in *Piper longum* respectively and in three identical laboratory batch of Thirikadu choornam name TC-I, TC-II and TC-III and marketed formulation were 1.852 ± 0.005, 1.843 ± 0.009, 1.831 ± 0.121 and 1.639 ± 0.852% w/w respectively. The HPTLC method developed is simple, accurate, and the statistical analysis proved that the method is reproducible and efficient for the analysis of piperine.

- **Stability studies**

  Accelerated stability studies were performed on the basis of physicochemical parameters viz. colour, odour, taste, moisture content, volatile oil content and piperine content. Throughout the duration of study little or insignificant observable changes are recorded and the formulations found stable for the length of time of study, i.e. 6 months.

5.4 **Standardization of Safoof-E-Sana**

Tibb-e-Unani (Unani medicine) claims to possess many safe and effective drugs, useful in various abdominal disorders. The formulations despite being widely used in the management of abdominal ailments have not been scientifically studied for their pharmacological effects and physicochemical evaluation for assurance of uniformity of the quality of formulations.
Safoof-E-Sana is a fine powder form (Unani Formulation), which is widely used as laxative at dose of 3-6 gm/day. It is composed of Burge Sana (Senna leaves), used in constipation, fever, skin diseases, and gout; Zanjabeel (dry ginger) used in asthma, diarrhea, cardiac diseases and wounds; Poste Haleel e zard (haritakee) used in cardiac diseases, jaundice, cough and carcinoma; and Namak e Siyah (balck salt) claims to posses laxative and carminative. The key ingredient of Safoof-E-Sana is senna leaves (Cassia angustifolia). All the ingredients are firstly powdered separately and mixed together. The genus senna is known to possess important medicinal properties, as it is a rich source of anthraquinones, flavonoids, polysaccharides, sterols and stilbenoids, showing a wide spectrum of biological activity. From the therapeutical point of view the most important characteristics is the laxative property. The biological activity is related to the contents of anthraquinones and flavonoids in this genus.

Three batches of Safoof-E-Sana designated as SS-I, SS-II and SS-III, were prepared in laboratory using method described in Unani Pharmacopoeia. These three batches of lab formulation and one marketed preparation were evaluated for organoleptic characters. The results for the marketed formulations M I and Laboratory formulation are found comparable.

The moisture content of Zingiber officinale, Cassia angustifolia, Terminalia chebula, lab formulation (SS-I) and marketed formulation were found 3.13±0.682, 3.34±0.445, 3.82±0.474, 3.25±0.582 and 3.93±0.323 % w/w respectively. The moisture content of formulation was within acceptable range (<8%) thus implying that the formulation can be stored for a long period and would not easily be attacked by microbes. Physical properties namely tapped density, bulk density, angle of repose, hausner ratio and carr’s index were calculated for Safoof-E-Sana and its raw materials. The value of angle of repose for raw materials Zingiber officinale, Cassia angustifolia, Terminalia chebula, Balck salt, lab formulation (SS-I) and marketed formulation were 34.48, 29.52, 28.92, 22.54, 27.68 and 26.68 respectively which shows good flow properties of prepared lab formulation. The flow properties are also confirmed by Hausner’s ratio and Carr’s index. Values of Hausner’s ratio less than 1.25 indicate good flow (20% Carr Index) and the value greater then 1.25 indicates poor flow (33%
Summary and Conclusion

Carr Index). The flow properties of lab (SS-I) and marketed formulations were also confirmed by Hausner’s ratio and Carr’s index; it was found 1.23, 19, and 1.27, 21.15 respectively and indicates good flow characteristics.

One notable difference as a result of the methods of extraction is the possibility that the alkaloids in Cassia angustifolia are more water soluble, the reason why the presence of that group was not detectable in the ethanolic extract. Furthermore, where more than one test was conducted for the detection of a chemical group such as the alkaloids, no differences in the results were observed for the different tests. Out of the nine phytochemical groups investigated, five namely carbohydrate, glycosides, tannins, and proteins were detected in the ethanolic extract of lab formulation and seven were present in the aqueous extract of lab formulation including alkaloids and saponins with previously stated five. Fixed oil and steroids were absent in all the ingredients and lab formulation for both methods of extraction.

Total ash value of Zingiber officinale, Cassia angustifolia, Terminalia chebula, lab formulation (SS-I) and marketed formulation were 5.023 ± 0.643, 7.023 ± 0.426, 3.891 ± 0.423, 19.146 ± 0.237 and 20.223 ± 0.336 respectively. The value of total ash in formulation is comparatively high because of the presence of black salt in formulation. Acid-insoluble ash value of lab formulation (SS-I) and marketed formulation were 2.351 ± 0.23 and 2.541 ± 0.056 which shows that a very small amount of the inorganic component is insoluble in acid it indicates adulteration of raw ingredients by substance like silica, rice husk is very less.

Higher water-soluble extractive value of lab and marketed preparation (45.784 ± 0.876 and 40.147 ± 1.654 respectively) implies that water is a better solvent of extraction for the formulation than ethanol.

● Spectrophotometric analysis

Safoof-E-Sana and Terminalia chebula is estimated spectrophotometrically for its gallic acid content against standard gallic acid solution on UV-Visible Spectrophotometer at λmax 271 nm. The concentration of gallic acid present in Terminalia chebula was 2.952 ± 0. 124 % w/w and in three identical laboratory batch of Safoof-E-Sana SS-I, SS-II and SS-III, it was found to be 0.704 ± 0. 012, 0.699 ±
0.114 and 0.702 ± 0.123 % w/w respectively. In marketed formulation the gallic acid content was found 0.612±0.151 % w/w. The method was validated statistically. The gallic acid content of all the three batches is found to be in close proximities with each other and recovery studies are indicative of reproducibility of method. The results were comparable to marketed formulations. Hence the present method is simple, and accurate and can be adopted for routine quality control of Safoof-E-Sana.

- **HPLC fingerprinting method**

The study is an attempt to develop the fingerprint method for Safoof-E-Sana by simple high-performance liquid chromatography (HPLC) determination using gallic acid as a standard, which are important and major content in formulation. RP- HPLC methods for simultaneous determination of gallic acid have been developed. A C 18 LUNA (5 micron 25 cm×4.6 mm) column from Phenomenex in binary gradient mode with mobile phase methanol at flow rate is 1.0ml/min used and effluent was monitored at 271 nm. Validation of the method was done with a view to demonstrate its selectivity, linearity, precision and accuracy. The content of gallic acid in *Terminalia chebula*, different batches of Safoof-E-Sana lab formulations (SS-I, SS-II, SS-III) and marketed formulation were found to be 3.145±0.013, 0.735 ± 0.012, 0.738 ± 0.016, 0.730 ± 0.015, 0.646 ± 0.062 % w/w respectively.

- **HPTLC fingerprinting method**

HPTLC fingerprint method for Safoof-E-Sana using gallic acid as a standard is developed. The gallic acid is an important content in the formulation and all of its herbal raw ingredients. The method was validated for linearity, accuracy, limit of detection, limit of quantification, inter-day and intra-day assay precision, repeatability of measurement, and repeatability of sample application. The content of gallic acid in *Terminalia chebula*, different batches of Safoof-E-Sana (SS-I, SS-II, SS-III) and marketed formulation were found 3.152 ± 0.002, 0.739 ± 0.011, 0.738 ± 0.018, 0.733 ± 0.011 and 0.649 ± 0.022 % w/w respectively. The statistical analysis proved that the method is reproducible and efficient for the analysis of gallic acid in formulations. These findings can be used as routine
chromatographic fingerprinting method for the standardization of the herbal raw materials as well as the finished formulation of Safoof-E-Sana.

- **Stability studies**

In the accelerated stability studies physicochemical parameters as per Who (1998) viz. colour, odour, taste, moisture content and gallic acid content were studied. The result of study reveals that there are no or little observable changes in the parameters during a time period of 6 months. It indicates that the formulations are stable under the different stability studies parameters.

5.5 Development of Modern dosage form (Capsule) of selected Indigenous formulations

In present study we have taken four traditional medicines and all are in powder (churna) form. We have developed the capsule dosage form for these four formulations to increase their dose accuracy, stability, convenience to handle, and over and all to improve their global acceptance. All the selected indigenous formulations have the dose of 500 to 1000 mg/day as per their official formularies. Hence they are very much suitable to be developed as capsule dosage form. The size of the capsule shell was selected Zero “0” as this size have the reported filling capacity between 500-600 mg.

- **Uniformity of weight**

Uniformity of weight were determined for the each selected formulations as per the method described above. The capsules produced were physically elegant and acceptable and met the pharmacopoeia specifications for content and weight uniformity (The average deviation in weight were 0.081±0.093, 0.108±0.093, 0.115±0.117 and 0.246±0.143 respectively for BC (Balacaturbhadrka churna), SC (Shringyadi churna), TC (Thirikadu choornam) and SS (Safoof-E-Sana). Results shows that all the capsule formulations complies with the Indian Pharmacopoeia range (<7.5%).
Summary and Conclusion

- **Disintegration time**

Disintegration time for each selected formulations BC (Balacurbhadrika churna), SC (Shringyadi churna), TC (Thirikadu choornam) and SS (Safoof-E-Sana) were estimated as per Indian Pharmacopoeia. Finding of disintegration time of above mentioned formulations were 5.20±0.480, 5.46±0.456, 5.10±0.431 and 5.35±0.009 respectively. Results were in the acceptable range (< 7 min).

- **Moisture content**

After the capsules were filled the moisture level of its contents were tested. The results of these tests indicated that the moisture level of the contents of the each formulations BC (Balacurbhadrika churna), SC (Shringyadi churna), TC (Thirikadu choornam) and SS (Safoof-E-Sana) were 3.02±0.34, 2.88±2.34, 2.70±3.32 and 3.96±3.45 respectively. The entire freshly prepared capsule shows moisture content at acceptable range (< 8%) as per WHO guidelines. Since the moisture absorbed may speed up degradation, the humidity conditions during the manufacture of the capsules can thus be a crucial factor and these capsules should preferably be manufactured under more tightly controlled humidity conditions.

- **Stability studies**

Following storage conditions were selected as per ICH guidelines which are long term storage condition (25°C/60% relative humidity (RH) for 12 months), accelerated conditions (40°C/75% RH) for 6 months and to reveal the effect of container we were also determined the moisture content outside the container at 25°C/60% relative humidity (RH) for 6 months.

- **25°C/60% relative humidity (RH) inside container**

Results shows that at 25°C/60% relative humidity (RH) inside container all the selected lab formulations do not posses the significant moisture content which was 3.31±0.55, 3.18±0.66, 3.09±0.23 and 4.72±0.54 for BC (Balacurbhadrika churna),
Summary and Conclusion

SC (Shringyadi churna), TC (Thirikadu choornam) and SS (Safoof-E-Sana) respectively. Hence it reflects that in this storage condition moisture content of each capsule was <5 % w/w which indicates that there is less chances of microbial growth and capsule will not become soft. Percent active ingredient was estimated with respect to its initial concentration present before storage in respective formulations. It was found 98.88±0.29, 97.89±0.43 and 96.91±0.87% w/w of piperine in BC, SC and TC respectively. Similarly for SS gallic acid was found 98.68±0.22 % w/w with respect to its concentration present in formulation before storage. The above results reveal that this storage condition is suitable for this developed capsule dosage form formulations.

- **25°C/60% relative humidity (RH) outside the containers**

At this condition all the formulations shows significant increase in the percent moisture content. It was 17.86±0.34, 17.51±0.43, 17.63±0.12 and 18.88±0.43 for BC (Balacaturbhadrika churna), SC (Shringyadi churna), TC (Thirikadu choornam) and SS (Safoof-E-Sana) respectively. Results at this condition reflect that powder is hygroscopic in nature and it should be kept inside the container immediately after the formulation. Percent active ingredient was estimated with respect to its initial concentration present before storage in respective formulations. It was found 91.20±0.41, 90.62±0.34 and 89.48±0.73 % w/w of piperine in BC, SC and TC respectively. Similarly for SS gallic acid was found 92.22±0.28 % w/w with respect to its concentration present in formulation before storage. The above results depict significant loss of active ingredients in formulations.

- **40°C/75% relative humidity (RH) inside containers**

This condition reveals that even inside the container, storage of the capsule in atmospheres of high humidity will increase the moisture content which typically accelerates decompositions that result from hydrolysis. Also, an increase in temperature causes an increase in the rate of chemical reaction. The results at this condition shows percent moisture content 8.84±0.12, 8.67±0.32, 8.50±0.87 and
Summary and Conclusion

10.03±0.12 for BC (Balacurbhadrika churna), SC (Shringyadi churna), TC (Thirikadu choornam) and SS (Safoof-E-Sana) respectively. Percent active ingredient was estimated with respect to its initial concentration present before storage in respective formulations. It was found 93.63±0.11, 92.28±0.85 and 90.61±0.32 % w/w of piperine in BC, SC and TC respectively. Similarly for SS gallic acid was found 91.11±0.48% w/w with respect to its concentration present in formulation before storage. The above result again shows significant loss of active ingredients in comparison with 25°C/60% relative humidity (RH) inside container storage condition.

Through these studies we can conclude that the capsule of each selected lab formulations passed the test for uniformity of weight. All capsules disintegrated within 7 minutes. Moisture content of capsule was <5 % w/w at 25°C/60% relative humidity (RH) inside container which indicates that there is less chances of microbial growth and capsule will not become soft and most important at this storage condition (25°C/60% relative humidity (RH) inside container) the amount of active ingredients was also found comparable with fresh formulation.

The present research work establishes the organoleptic, physicochemical, phytochemical and fingerprinting aspects of selected traditional indigenous formulations. The above established quality control parameters ensures the quality, safety, and efficacy of selected formulations and hence their global acceptance. This work also gives guidelines for the standardization of other indigenous formulations with the help of standard marker compounds. On the other hand development of modern dosage forms like capsule increase their dose accuracy, stability, convenience to handle and worldwide recognition.
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List of Publication


4. Legal regulations of complementary and alternative medicines in different countries. Pharmacognosy Reviews (Article in Press).


Papers presented in conferences


Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) for plant actives and extracts. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. The present review highlights the current status of the development of novel herbal formulations and summarizes their method of preparation, type of active ingredients, size, entrapment efficiency, route of administration, biological activity and applications of novel formulations.

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Keywords: Herbal drugs Novel drug delivery systems (NDDS)
dosage forms (polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes and nanoemulsion etc.) have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improving tissue macropores distribution, sustained delivery, protection from physical and chemical degradation etc. Thus the nano sized novel drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines. Liposomes, which are biodegradable and essentially non-toxic vehicles, can encapsulate both hydrophilic and hydrophobic materials [1]. Liposome based drug delivery systems offer the potential to enhance the therapeutic index of anti-cancer agents, either by increasing the drug concentration in tumor cells and/or by decreasing the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon and by utilizing targeting strategies [2]. The main advantages of using liposomes include: i) the high biocompatibility, ii) the easiness of preparation, iii) the chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds, and iv) the simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components [3]. Delivery of agents to the reticuloendothelial system (RES) is easily achieved, since most conventional liposomes are trapped by the RES [1]. The application of novel approaches can also improve the efficacy of herbal cosmetic formulations on the human body [4]. Similarly the other vesicular systems like nanoemulsion, ethosomes and transferosomes are highly useful assemblies and find various advantages in the delivery of herbal medicines; some of them are summarized in present article.

The phytosome process has also been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milk thistle [5], green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosome is produced by binding individual components of herbal extracts to phosphatidylcholine, resulting in a dosage form that is better absorbed and thus, produces better results than the conventional herbal extracts [6]. The results indicate that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract [5]. Drugs can be embedded or dissolved in nanoparticles and can also be adsorbed or coupled on the surface [7]. Encapsulating drugs within NPs can improve the solubility and pharmacokinetics of drugs, and, in some cases, enable further clinical development of new chemical entities that have stalled because of poor pharmacokinetic properties [8]. The major carrier materials of nanoparticles are synthetic biodegradable high molecular polymer and natural polymer. The former usually includes poly-α-cyanoacrylate alkyl esters, polyvinyl alcohol, polyactic acid, and polyactic-glycolic acid, etc. The latter is usually divided into two classes: proteins (albumin, gelatin and vegetable protein) and polysaccharides (cellulose, starch and its derivatives, alginate, chitin and chitosan, etc.) [9].

In this article, an attempt has been made to touch upon different aspects related to the development of novel herbal formulations, including method of preparation, type of active ingredient, entrapment efficiency, and applications etc.

2. Liposome

The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse (float) into their interior. They can have one, several or multiple concentric membranes. Liposomes are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules [10]. Upon interaction with water, polar lipids self-assemble and form self-organized colloidal particles. Simple examples are detergents, components form micelles, while polar lipids with bulkier hydrophobic parts cannot associate into micelles with high curvature radii but form bilayers which can self-close into liposomes or lipid vesicles. A cross-section of a liposome (Fig. 1) depicts the hydrophilic heads of the amphiphile orienting towards the water compartment while the lipophilic tails orient away from the water towards the center of the vesicle, thus forming a bilayer. Consequently, water soluble compounds are entrapped in the water compartment and lipid soluble compounds aggregate in the lipid section. Uniquely, liposomes can encapsulate both hydrophilic and lipophilic materials. Liposomes usually formed from phospholipids, have been used to change the pharmacokinetics profile of, not only drugs, but herbs, vitamins and enzymes. A variety of herbal liposomal formulations has been studied which are summarized in Table 1. Because of their unique properties liposomes are able to enhance the performance of products by increasing ingredient solubility, improving ingredient bioavailability, enhanced intracellular uptake and altered pharmacokinetics and biodistribution [9] and in vitro and in vivo stability. Liposomes as a drug delivery system can improve the therapeutic activity and safety of drugs, mainly by delivering them to their site of action and by maintaining therapeutic drug levels for prolonged periods of time [11–13].

Milk thistle (Silybum marianum) is one of the few herbal drugs whose excellent pharmacological profile readily lends itself to proof of clinical efficacy [13]. Meanwhile, silymarin is poorly absorbed (20–50%) from the gastrointestinal tract [14] that causes the effects of silybin, one of the main active flavonoids commonly found in the dried fruits of silymarin, to be greater after parenteral than oral administration [15].
Incorporation of silymarin into liposomal dosage form administered buccally can improve its bioavailability. In this connection to improve the bioavailability of silymarin through its incorporation in a stable liposomal dosage form, using commercially available soybean lecithin. El-Samaligy et al. [16] prepared silymarin encapsulated hybrid liposomes which shows successful preparation with efficient encapsulation of silymarin. Mixing silymarin loaded hybrid liposomes with unloaded ones in a (1:1) proportion was useful in prevention of aggregates which threaten liposomal stability. M50 proved stability regarding encapsulation efficiency, turbidity measurement and particle size analysis after 3 months of storage at 4 °C or at ambient temperature. Refrigeration is recommended to achieve better stability. The introduced hybrid liposomal silymarin formula for buccal administration have the advantages of exerting a mucoadhesive effect [17] besides its deformability due to the presence of Tween 20 as edge activator allowing the medicated liposomes to squeeze through buccal mucosal cells. It was also shown to be safe upon contacting the rat buccal mucosa.

### Table 1
Liposomal herbal formulation.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Active ingredients</th>
<th>Applications of liposome formulations</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>% Entrapment efficiency</th>
<th>Route of administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin liposomes</td>
<td>Quercetin</td>
<td>Reduced dose, enhance penetration in blood brain barrier</td>
<td>Antioxidant, Anticancer</td>
<td>Reverse evaporation technique</td>
<td>60%</td>
<td>Intranasal</td>
<td>[18]</td>
</tr>
<tr>
<td>Liposomes encapsulated silymarin</td>
<td>Silymarin</td>
<td>Improve bioavailability</td>
<td>Hepatoprotective</td>
<td>Reverse evaporation technique</td>
<td>69.22±0.6%</td>
<td>Buccal</td>
<td>[16]</td>
</tr>
<tr>
<td>Liposoma artemisia arborescens</td>
<td>Artemisia arborescens essential oil</td>
<td>Targeting of essential oils to cells, enhance penetration into, cytoplasmatic barrier</td>
<td>Antiviral</td>
<td>Film method and sonication</td>
<td>60–74%</td>
<td>In vitro</td>
<td>[19]</td>
</tr>
<tr>
<td>Ampelopsin liposome</td>
<td>Ampelopsin</td>
<td>Increase efficiency</td>
<td>Anticancer</td>
<td>Film-ultrasound method</td>
<td>62.30%</td>
<td>In vitro</td>
<td>[20]</td>
</tr>
<tr>
<td>Paclitaxel liposome</td>
<td>Paclitaxel</td>
<td>High entrapment efficiency and pH sensitive</td>
<td>Anticancer</td>
<td>Thin film hydration method</td>
<td>94%</td>
<td>In vitro</td>
<td>[21]</td>
</tr>
<tr>
<td>Curcumin liposome</td>
<td>Curcumin</td>
<td>Long-circulating with high entrapment efficiency</td>
<td>Anticancer</td>
<td>Ethanol injection method</td>
<td>88.27±2.16</td>
<td>In vitro</td>
<td>[22]</td>
</tr>
<tr>
<td>Garlicin liposome</td>
<td>Garlicin</td>
<td>Increase efficiency</td>
<td>Lungs</td>
<td>Reverse-phase evaporation method</td>
<td>90.77 %</td>
<td>–</td>
<td>[23]</td>
</tr>
<tr>
<td>Flavonoids liposomes</td>
<td>Quercetin and rutin</td>
<td>Binding of flavonoids with Hb is enhanced</td>
<td>Hemoglobin</td>
<td>Solvent evaporation</td>
<td>–</td>
<td>In vitro</td>
<td>[24]</td>
</tr>
<tr>
<td>Usnea acid liposome with β-CD</td>
<td>Usnea acid</td>
<td>Increase solubility and localization with prolonged-release profile</td>
<td>Antimycobacterial</td>
<td>Hydration of a thin lipid film method with sonication</td>
<td>99.5%</td>
<td>In vitro</td>
<td>[25]</td>
</tr>
<tr>
<td>Wogonin liposome</td>
<td>Wogonin</td>
<td>Sustained release effect</td>
<td>Anticancer</td>
<td>Film dispersion method</td>
<td>81.20±4.20%</td>
<td>In vivo</td>
<td>[26]</td>
</tr>
<tr>
<td>Colchicine Liposome</td>
<td>Colchicine</td>
<td>Enhance skin accumulation, prolong drug release and improve site specificity</td>
<td>Antigout</td>
<td>Rotary evaporation sonication method</td>
<td>66.3±2.2%</td>
<td>Topical</td>
<td>[27]</td>
</tr>
<tr>
<td>Catechins liposomes</td>
<td>Catechins</td>
<td>Increased permeation through skin</td>
<td>Antioxidant and chemopreventive</td>
<td>Rotary evaporation sonication method</td>
<td>93.0±0.1</td>
<td>Transdermal</td>
<td>[28]</td>
</tr>
<tr>
<td>Breviscapine liposomes</td>
<td>Breviscapin</td>
<td>Sustained delivery of breviscapine</td>
<td>Cardiovascular diseases</td>
<td>Double emulsification process</td>
<td>87.9±3.1%</td>
<td>Intramuscular</td>
<td>[29]</td>
</tr>
</tbody>
</table>

### Table 2
Nanoparticles and nanoemulsions (Fig. 2) are colloidal systems with particles varying in size from 10 nm to 1000 nm [31,32]. Nanoparticle systems with mean particle size well above the 100 nm standard have also been reported in literature, including nanonized curcuminoids [33], paclitaxel [34] and praziquantel [35] which have a mean particle size of 450, 147.7, and even higher than 200 nm, respectively. In addition, nanoparticles could also be defined as being submicronic (≤1 lm) colloidal systems [36]. The nanospheres have a matrix type structure in which the active ingredient is dispersed throughout (the particles), whereas the nanocapsules have a polymeric membrane and an active ingredient core. Nanonization possesses many advantages, such as increasing compound solubility, reducing medicinal doses, and improving the absorbency of herbal medicines compared with the respective crude drugs preparations [36].

### 3. Nanoparticles
In recent year, the nanonization of herbal medicines has attracted much attention; [30] some of them are illustrated in

### 4. Phytosome
Over the past century, phytochemical and phytopharmaceutical sciences established the compositions, biological activities and health promoting benefits of numerous plant products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, terpenoids, etc.)
<table>
<thead>
<tr>
<th>Formulations</th>
<th>Active ingredients</th>
<th>Applications of nanostructured formulations</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>% Entrapment efficiency</th>
<th>Route of administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptolide nanoparticle</td>
<td>Triptolide</td>
<td>Enhance the penetration of drugs through the stratum corneum by increased hydration</td>
<td>Anti-inflammatory</td>
<td>Emulsification-ultrasound</td>
<td>–</td>
<td>Topical (skin)</td>
<td>[30]</td>
</tr>
<tr>
<td>Nanoparticles of Cuscuta chinensis</td>
<td>Flavonoids and lignans</td>
<td>Improve water solubility, Decreasing the toxicity</td>
<td>Hepatoprotective and antioxidant effects</td>
<td>Nanosuspension method</td>
<td>90%</td>
<td>Oral</td>
<td>[37]</td>
</tr>
<tr>
<td>Triptolide-loaded solid lipid nanoparticle</td>
<td>Triptolide</td>
<td>Decreasing the toxicity</td>
<td>Anti-inflammatory</td>
<td>Emulsification-ultrasound</td>
<td>–</td>
<td>Oral</td>
<td>[38]</td>
</tr>
<tr>
<td>Artemisinin nanocapsules</td>
<td>Artemisinin</td>
<td>Sustained drug release</td>
<td>Anticancer</td>
<td>Self-assembly procedure</td>
<td>90–93%</td>
<td>In vitro</td>
<td>[39]</td>
</tr>
<tr>
<td>Radix salvia miltiorrhiza nanoparticles</td>
<td>R. salvia miltiorrhiza</td>
<td>Improve the bioavailability</td>
<td>Coronary heart diseases, angina pectoris and myocardial infarction</td>
<td>Spray-drying technique</td>
<td>Upto 96.68%</td>
<td>In vitro</td>
<td>[40]</td>
</tr>
<tr>
<td>Taxol-loaded nanoparticles</td>
<td>Taxol</td>
<td>Enhance the bioavailability and sustained drug release</td>
<td>Anticancer</td>
<td>Emulsion solvent evaporation method</td>
<td>99.44%</td>
<td>–</td>
<td>[41]</td>
</tr>
<tr>
<td>Berberine-loaded nanoparticles</td>
<td>Berberine</td>
<td>Sustained drug release</td>
<td>Anticancer</td>
<td>Ionic gelation method</td>
<td>65.40 ± 0.70%</td>
<td>In vitro</td>
<td>[42]</td>
</tr>
<tr>
<td>Silibini-loaded nanoparticles</td>
<td>Silibini</td>
<td>High entrapment efficiency and stability Sustained drug release</td>
<td>Hepatoprotective</td>
<td>High pressure homogenization and solvent evaporating</td>
<td>95.64%</td>
<td>–</td>
<td>[43]</td>
</tr>
<tr>
<td>Terrandrine-loaded nanoparticles</td>
<td>Terrandrine</td>
<td>Increase antioxidant activity and release of the drug 74 times higher</td>
<td>Anti-inflammatory, antihypertensive</td>
<td>Nanoprecipitation technique over 99%</td>
<td>84%</td>
<td>In vitro</td>
<td>[44]</td>
</tr>
<tr>
<td>Glycyrrhizin acid-loaded nanoparticles</td>
<td>Glycyrrhizin acid</td>
<td>Improve the bioavailability</td>
<td>Cardiovascular and cerebrovascular</td>
<td>Spontaneous emulsification-solvent diffusion technique</td>
<td>93.1%</td>
<td>Intra Venous</td>
<td>[45]</td>
</tr>
<tr>
<td>Quercetin-loaded nanoparticles</td>
<td>Quercetin</td>
<td>Increase antioxidant activity and release of the drug 74 times higher</td>
<td>Antioxidant</td>
<td>Nanoprecipitation technique over 99%</td>
<td>–</td>
<td>Oral</td>
<td>[46]</td>
</tr>
<tr>
<td>Brevicapine-loaded nanoparticles</td>
<td>Brevicapine</td>
<td>Prolong the half-life and decrease RES uptake</td>
<td>Cardiovascular and cerebrovascular</td>
<td>Spontaneous emulsification-solvent diffusion technique</td>
<td>93.1%</td>
<td>Intra Venous</td>
<td>[47]</td>
</tr>
<tr>
<td>Zedoary turmeric oil nanocapsule</td>
<td>Zedoary turmeric oil</td>
<td>Increase the drug loading and stability of ZTO</td>
<td>Hepatoprotection Anticancer and anti-bacterial</td>
<td>High pressure homogenization method</td>
<td>1.62 ± 0.15%</td>
<td>–</td>
<td>[48]</td>
</tr>
<tr>
<td>Naringenin-loaded nanoparticles</td>
<td>Naringenin</td>
<td>Improved the release of NAR and improved its solubity</td>
<td>Hepatoprotective</td>
<td>Nanoprecipitation method –</td>
<td>–</td>
<td>Oral</td>
<td>[49]</td>
</tr>
<tr>
<td>Curcuminoids solid lipid nanoparticles</td>
<td>Curcuminoids</td>
<td>Prolonged-release of the curcuminoids</td>
<td>Anticancer and antioxidant</td>
<td>70%</td>
<td>–</td>
<td>In vitro</td>
<td>[50]</td>
</tr>
<tr>
<td>CPT-encapsulated nanoparticles</td>
<td>Camptothecin</td>
<td>Prolonged blood circulation and high accumulation in tumors</td>
<td>Anticancer</td>
<td>Dialysis method</td>
<td>&gt;80%</td>
<td>In vitro</td>
<td>[51]</td>
</tr>
<tr>
<td>Ginkgo biloba nanoparticles</td>
<td>Ginkgo biloba extract</td>
<td>Improving the cerebral blood flow and metabolism</td>
<td>Brain function activation</td>
<td>High pressure homogenization method</td>
<td>–</td>
<td>Oral</td>
<td>[52]</td>
</tr>
</tbody>
</table>
Table 3
Phytosomal herbal formulations.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Active ingredients</th>
<th>Applications of phytosomal formulations</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba phytosome</td>
<td>Flavonoids</td>
<td>Flavonoids of GBP stabilize the ROS</td>
<td>Cardio-protective, antioxidant activity</td>
<td>Phospholipids complexation</td>
<td>100 mg and 200 mg/kg</td>
<td>Oral</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibits lipid peroxidation (LPO),</td>
<td>Hepatoprotective, antioxidant</td>
<td>Phospholipids complexation</td>
<td>25 and 50 mg/kg</td>
<td>Oral</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stabilize the ROS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgoselect phytosome</td>
<td>Flavonoids</td>
<td>Flavonoids</td>
<td>Hepatoprotective, antioxidant for liver and skin</td>
<td>Silybin-phospholipid complexation</td>
<td>120 mg</td>
<td>Oral</td>
<td>[57]</td>
</tr>
<tr>
<td>Silybin phytosome</td>
<td>Flavonoids</td>
<td>Absorption of silybin phytosome from</td>
<td>Nutraceutical, immunomodulator</td>
<td>Phospholipids complexation</td>
<td>150 mg</td>
<td>Oral</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>silybin is approximately seven times</td>
<td>Nutraceutical, systemic antioxidant, anti-cancer</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>greater</td>
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</tr>
<tr>
<td>Ginseng phytosome</td>
<td>Ginsenosides</td>
<td>Increase absorption</td>
<td>Nutraceutical, systemic antioxidant, anti-cancer</td>
<td>Phospholipids complexation</td>
<td>50–100 mg</td>
<td>Oral</td>
<td>[58]</td>
</tr>
<tr>
<td>Green tea phytosome</td>
<td>Epigallocatechin</td>
<td>Increase absorption</td>
<td>Nutraceutical, systemic antioxidant, anti-cancer</td>
<td>Phospholipids complexation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Grape seed phytosome</td>
<td>Procyanidins</td>
<td>The blood TRAP nTotal Radical-trapping</td>
<td>Systemic antioxidant, cardio-protective and antihypertensive Antioxidant, anticaner</td>
<td>Phospholipids complexation</td>
<td>50–100 mg</td>
<td>Oral</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antioxidant Parameter) were significantly elevated over the control</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Increase therapeutic efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and absorption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawthorn Phytosome</td>
<td>Flavonoids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quercetin phytosome</td>
<td>Quercetin</td>
<td>Exerted better therapeutic efficacy</td>
<td>Antioxidant, anticancer</td>
<td>Quercetin–phospholipid complexation</td>
<td>–</td>
<td>Oral</td>
<td>[59]</td>
</tr>
<tr>
<td>Curcumin phytosones</td>
<td>Curcumin</td>
<td>Increase antioxidant activity and</td>
<td>Antioxidant, anticancer</td>
<td>Curcumin–phospholipid complexation</td>
<td>360 mg/kg</td>
<td>Oral</td>
<td>[60],[49]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase bioavailability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naringenin phytosones</td>
<td>Naringenin</td>
<td>Prolonged duration of action</td>
<td>Antioxidant activity</td>
<td>Naringenin–phospholipid complex</td>
<td>100 mg/kg</td>
<td>Oral</td>
<td>[61]</td>
</tr>
</tbody>
</table>
Phytosome has been an emerging trend in delivery of herbal drugs and nutraceuticals.

5. Emulsions

Emulsion refers to a non-homogeneous dispersion system that is composed of two kinds of liquids unable to dissolve each other, and one of which disperse in the other one in a form of droplets [62]. Generally, emulsion is composed of oil phase, water phase, surfactant and sub-surfactant. Its appearance is translucent to transparent liquid. Emulsion can be classified into ordinary emulsion (0.1–100 μm), micro-emulsion (10–100 nm), sub-micro-emulsion (100–600 nm), etc. (Table 4). Among them, the micro-emulsion is also called nanoemulsions, and the sub-micro-emulsion is also called lipid emulsion. As a drug delivery system, emulsion distributes in vivo in the targeted manner due to its affinity to the lymph. In addition, the drug can be sustained release in a long time because the drug is packaged in the inner phase and kept off direct touch with the body and tissue fluid [63]. After the oily drugs or lipophilic drugs being made into O/W or O/W/O emulsion, the oil droplets are phagocytosised by the macrophage and get a high concentration in the liver, spleen, and kidney in which the amount of the dissolved drug is very large. While water soluble drug is produced into W/O or W/O/W emulsion, it can be easily concentrated in the lymphatic system by intramuscular or subcutaneous injection. The size of the emulsion particle has an impact on its target distribution.

Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous, and reduce the drugs’ stimulus to tissues. So far, some kinds of herbal drugs, such as camptothecin, Brucea javanica oil, coixenolide oil and zedoary oil have been made into emulsion. For example, Zhou et al. [64] studied the influence of the elemenum emulsion on the human lung adenocarcinoma cell line A549 and protein expression. Results showed that the elemenum emulsion has a significant inhibition on the growth and proliferation of the A549 in vitro and it showed a time and dose-dependent relationship. Elemenum emulsion is a type of new anti-cancer drug with great application prospects. Furthermore, it has no marrow inhibition and no harm to the heart and liver.

Table 4
Emulsion herbal formulations.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Active ingredients</th>
<th>Applications of emulsion formulations</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Droplet size</th>
<th>Drug loading</th>
<th>Route of administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-nanoemulsifying Zedoary</td>
<td>Zedoary turmeric</td>
<td>Improved aqueous dispersibility,</td>
<td>Hepatoprotection</td>
<td>Drawing ternary phase diagram</td>
<td>68.3±1.5 nm</td>
<td>30%</td>
<td>Oral</td>
<td>[65]</td>
</tr>
<tr>
<td>essential oil</td>
<td>oil</td>
<td>stability and oral bioavailability</td>
<td>anticancer and anti-bacterial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triptolide micro-emulsion</td>
<td>Triptolide</td>
<td>Enhance the penetration of drugs</td>
<td>Anti-inflammatory</td>
<td>High pressure Homogenization method</td>
<td>&lt;100 nm</td>
<td>–</td>
<td>Topical</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>through the stratum corneum and</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased hydration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel submicron emulsion</td>
<td>Docetaxel</td>
<td>Improve residence time</td>
<td>Anticancer</td>
<td>High pressure Homogenization method</td>
<td>166.00 nm</td>
<td>90%</td>
<td>Intravenous</td>
<td>[66]</td>
</tr>
<tr>
<td>Berberine nanoemulsion</td>
<td>Berberine</td>
<td>Improve residence time and absorption</td>
<td>Anticancer</td>
<td>Drawing ternary phase diagram</td>
<td>56.80 nm</td>
<td>0.50%</td>
<td>Oral</td>
<td>[67]</td>
</tr>
<tr>
<td>Silybin nanoemulsion</td>
<td>Silybin</td>
<td>Sustained release formulation</td>
<td>Hepatoprotective</td>
<td>Emulsification method</td>
<td>21.20 nm</td>
<td>–</td>
<td>Intramuscular</td>
<td>[68]</td>
</tr>
<tr>
<td>Quercetin micro-emulsion</td>
<td>Quercetin</td>
<td>Enhance penetration into stratum</td>
<td>Antioxidant</td>
<td>High speed Homogenization method</td>
<td>10–100 nm</td>
<td>0.3% solution</td>
<td>Topical</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>corneum and epidermis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Other novel vesicular herbal formulations

Transferosomes are applied in a non-occluded method to the skin, which permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. It can be applicable as drug carriers for a range of small molecules, peptides, proteins and herbal ingredients. Transferosomes can penetrate stratum corneum and supply the nutrients locally to maintain its functions resulting maintenance of skin [70] in this connection the transferosomes of Capsaicin has been prepared by Xiao-Ying et al. [71] which shows the better topical absorption in comparison to pure capsaicin. Ethisome, as a novel liposome, is especially suitable as a topical or transdermal administration carrier [72,73]. Ethisome has a high deformability and entrapment efficiency and can penetrate through the skin completely and improve drug delivery through the skin. Compared to other liposomes, the physical and chemical properties of ethisomes make the delivery of the drug through the stratum corneum into a deeper skin layer efficiently or even into the blood circulation [74]. This property is very important as the topical drug carrier and transdermal delivery system. Moreover, the ethisomes carrier also can provide an efficient intracellular delivery for both hydrophilic and lipophilic drugs [75], percutaneous absorption of matrine an anti-inflammatory herbal drug is increased; [76] it also permits the antibacterial peptide to penetrate into the fibrocyte easily [77]. The roles of these types of novel vascular system over herbal drug delivery are summarized in (Table 5).

7. Microspheres

Administration of medication via micro particulate systems is advantageous because microspheres can be ingested or injected and; they can be tailored for desired release profiles and used site-specific delivery of drugs and in some cases can even provide organ-targeted release [80]. So far, a series of plant active ingredients, such as rutin, camptothecin, zedoary oil, tetrandrine, quercetine and Cynara scolymus extract has been made into microspheres (Table 6). In addition, reports on immune microsphere and magnetic microsphere are also common in recent years. Immune microsphere possesses the immune competence as a result of the antibody and antigen was coated or adsorbed on the polymer microspheres.

8. Proprietary novel drug delivery system of plant actives and extracts

Cosmetochem International AG is a Swiss-based company, specialized in the production of high quality, customized botanical extracts and actives, launch botanical, standardized, liposomal powders named Liposome Herbasec® [86] a novel range of standardized botanical extracts in a liposomal-based powder form. As the liposome carriers are very effective penetration enhancers which serve as carriers to the skin, increasing the bioavailability of the plant extracts. In present formulation the freeze-dried dispersion of Liposome Herbasec® is reformed when dispersed in water, re-encapsulating

Table 5
Other novel vesicular herbal formulations.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Active ingredients</th>
<th>Applications</th>
<th>Biological activity</th>
<th>Droplet size</th>
<th>Route of administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin transferosomes</td>
<td>Capsaicin</td>
<td>Increase skin penetration</td>
<td>Analgesic</td>
<td>150.6 nm</td>
<td>Topical</td>
<td>[71]</td>
</tr>
<tr>
<td>Colchicine transferosomes</td>
<td>Colchicine</td>
<td>Increase skin penetration</td>
<td>Anti-gout</td>
<td>120 nm</td>
<td>In vitro</td>
<td>[77]</td>
</tr>
<tr>
<td>Vincristine transferosomes</td>
<td>Vincristine</td>
<td>Increase entrapment efficiency and skin permeation</td>
<td>Anti-cancer</td>
<td></td>
<td>In vitro</td>
<td>[77]</td>
</tr>
<tr>
<td>Matrine ethisome</td>
<td>Matrine</td>
<td>Improve the percutaneous permeation</td>
<td>Anti-inflammatory</td>
<td>110±8 nm</td>
<td>Topical</td>
<td>[76]</td>
</tr>
<tr>
<td>Ammonium glycyrrhizinate</td>
<td>Ammonium glycyrrhizate</td>
<td>Increase of the in vitro percutaneous permeation</td>
<td>Anti-inflammatory</td>
<td>350 nm to 100 nm</td>
<td>Topical</td>
<td>[78]</td>
</tr>
</tbody>
</table>

Table 6
Microspheres encapsulated herbal formulations.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Active ingredients</th>
<th>Applications</th>
<th>Biological activity</th>
<th>Method of preparation</th>
<th>Size in μm</th>
<th>Route of administration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutin–alginate–chitosan</td>
<td>Rutin</td>
<td>Targeting into cardiovascular and cerebrovascular region</td>
<td>Cardiovascular and Cerebrovascular diseases</td>
<td>Complex-coacervation method</td>
<td>165.00–195.00</td>
<td>In vitro</td>
<td>[81]</td>
</tr>
<tr>
<td>microcapsules</td>
<td></td>
<td></td>
<td>Hepatoprotective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zedoary oil microsphere</td>
<td>Zedoary oil</td>
<td>Sustained release and Higher bioavailability</td>
<td></td>
<td>Quasi-emulsion–solvent diffusion method</td>
<td>100–600</td>
<td>Oral</td>
<td>[82]</td>
</tr>
<tr>
<td>CPT loaded microspheres</td>
<td>Camptothecin</td>
<td>Prolonged-release of camptothecin</td>
<td>Anticancer</td>
<td>Oil-in-water evaporation method</td>
<td>10</td>
<td>Intraperitoneally and intravenously</td>
<td>[83]</td>
</tr>
<tr>
<td>Quercetin microspheres</td>
<td>Quercetin</td>
<td>Significantly decreases the dose size</td>
<td>Anticancer</td>
<td>Solvent evaporation method</td>
<td>6</td>
<td>In vitro</td>
<td>[84]</td>
</tr>
<tr>
<td>Cynara scolymus microspheres</td>
<td>Cynara scolymus extract</td>
<td>Controlled release of neutraceuticals</td>
<td>Nutritional supplement</td>
<td>Spray-drying technique</td>
<td>6–7</td>
<td>Oral</td>
<td>[85]</td>
</tr>
</tbody>
</table>
the concentrated plant extract. Phospholipids used for the preparation of formulation are the safest, mildest substances which allow the penetration of the plant actives into the deeper layers of the epidermis and avoid the use of solvents. There are five extracts in the current Liposome Herbasec® range (Table 7) which are standardized for specific phytochemicals. White and green tea are standardized for caffeine and total polyphenols, white hibiscus for fruit acids, guarana for caffeine and aloe vera is aloin-free [86]. Liposome Herbasec® can be used in a wide range of personal care applications. Similarly based on Phytosome® technology, a line of products has been developed and commercialized by Indena [87] (Table 7). The Phytosome® formulation increases the absorption of active ingredients when topically applied on the skin [88-97], and improves systemic bioavailability when administered orally [98-102]. A Phytosome® is generally more bioavailable than a simple herbal extract due to its enhanced capacity to cross the lipid-rich biomembranes and reach circulation [103-105]. To overcome the poor bioavailability of silybin, Indena has complexed it with soy phosphatidylcholine [108]. A lot of work that has been published in the journal Cancer Chemotherapy and Pharmacology [109] demonstrated Meriva®’s superior bioavailability compared to a standardized curcumin extract in rats, while very promising initial preclinical results in terms of improved hydrolytical stability and human pharmacokinetics have been shown more recently [108]. Including the advantages of these above mentioned commercialized NDDS preparation of plant actives/extracts a variety of other preparations is also available (Table 7) which show the remarkable advantages over pure plant actives/extracts.

9. Conclusion

An extensive research is going on in the area of novel drug delivery and targeting for plant actives and extracts. However, research in this area is still at the exploratory stage. Many problems in the research, production and application
need to be solved. In addition, more attention should be paid to the research on the carrier materials in order to develop more suitable carriers which can reduce the toxicity of drugs, enhance their activity and improve the overall quality of the agents. Herbal drugs have enormous therapeutic potential which should be explored through some value added drug delivery systems. Lipid solubility and molecular size are the major limiting factors for drug molecules to pass the biological membrane to be absorbed systemically following oral or topical administration. Several plant extracts and phytoconstituents, despite having excellent bio-activity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when administered through novel drug delivery system show much better absorption profile which enables them to cross the biological membrane, resulting enhanced bioavailability. Hence more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney, etc.) at similar or less dose as compared to the conventional plant extract or phytoheme. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered using NDDS. Hence there is a great potential in the development of novel drug delivery systems for the plant actives and extracts.

Acknowledgements

The authors acknowledge the University Grant Commission [F. no. 34-131/2008 (SR)], New Delhi, INDIA, for financial support.

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Legal regulations of complementary and alternative medicines in different countries

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Submitted: 25-03-2011 Revised: **-**-**** Published: **-**-****

ABSTRACT

Traditional medicines that formed the basis of health care throughout the world since the earliest days of mankind are still widely used and have considerable importance in international trade. Recognition of their clinical, pharmaceutical, and economic value is still growing, although this varies widely between countries and therefore regulation of exploitation and exportation is essential, together with international cooperation and coordination for their conservation so as to ensure their availability for the future. World Health Organization and European Union issued the guidelines defined the basic criteria for the evaluation of quality, safety, and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations, and manufacturers in assessing documentation, submissions, and dossiers in respect of such products. Legislative controls in respect of medicinal plants have not evolved around a structured control model. There are different ways in which countries define medicinal plants or herbs or products derived from them. The present review highlights the status of different countries adopted various approaches to licensing, dispensing, manufacturing, and trading to ensure their safety, quality, and efficacy.

Key words: Efficacy, legislation, quality, safety, traditional medicines

INTRODUCTION

During the past decade, complementary and alternative medicines have become a topic of global importance. Current estimates suggest that in many developing countries, a large proportion of the population relies heavily on traditional practitioners and medicinal plants to meet primary healthcare needs. Although modern medicine may be available in these countries, herbal medicines (phytomedicines) have often maintained popularity for historical and cultural reasons. Concurrently, many people in developed countries have begun to turn to alternative or complementary therapies, including medicinal herbs. World Health Organization (WHO) estimated that the world market for herbal medicines and herbal products is worth US$ 62 billion and would hit US$ 5 trillion by 2050. The market is growing at 7% per annum (The Times of India, 7-4-2000).

A common feature of most systems of traditional medicine (TM)/complementary and alternative medicine (CAM) is that they take a holistic approach to promote health, prevent disease, and help the individual treat disturbances by regulating his/her physical, emotional, and mental aspects and living environment. According to its characteristics and concepts, TM/CAM can be used not only for curing disease and relieving symptoms but also for the regulation, improvement, and promotion of the function of the human body. Few plant species that provide medicinal herbs have been scientifically evaluated for their possible medical application. Safety and efficacy data are available for even fewer plants, their extracts and active ingredients, and the preparations containing them. Furthermore, in most countries the herbal medicines’ market is poorly regulated, and herbal products are often neither registered nor controlled. Assurance of the safety, quality, and efficacy of medicinal plants and herbal products has now become a key issue in industrialized and in developing countries. Both the general consumer and healthcare professionals need up-to-date, authoritative information on the safety and efficacy of medicinal plants. With the widespread use of TM as well as CAM and the rapid expansion of international herbal medicine markets, the development of national policies and regulations on TM/CAM has become an important concern for both health authorities and the public. Providers of TM/CAM, other healthcare professionals, and TM/CAM consumers alike are calling for regulations that can ensure the safety of TM/CAM therapies and products, promote recognition of these systems and modalities, and further define their role in
modern healthcare systems. National policies and regulations on TM/CAM could ensure the safety, quality, and efficacy of these therapies and products and function as important steps toward integrative healthcare systems. However, relatively few countries have developed policies and regulations on TM/CAM so far. Only 25 of WHO’s 191 countries have a national policy on TM/CAM and only 64 countries regulate herbal medicines.\[1\]

To assist countries in the development of TM/CAM policies and regulations of herbal medicines, WHO has published a series of technical guidelines and reviewed regulations on herbal medicines in the document “Regulatory Situation of Herbal Medicines: a Worldwide Review.”[2] The purpose of the document is to share national experience in formulating policies on traditional medicinal products, introduce measures for their registration and regulation, and facilitate information exchange on these subjects among Member States.

In present review, we have compiled name of various regulatory authorities made for herbal medicines in different countries with their major responsibilities and year of establishment which will definitely help the new researchers working in the field of quality control and standardization of TM/CAM.

The role of herbal medicines in traditional healing
The pharmacological treatment of disease began long ago with the use of herbs.[3] Methods of folk healing throughout the world commonly used herbs as part of their tradition. Some of these traditions are briefly described below, providing some examples of the array of important healing practices around the world that used herbs for this purpose.[4]

Traditional Chinese medicine
Traditional Chinese medicine has been used by Chinese people from ancient times. Although animal and mineral materials have been used, the primary source of remedies is botanical. Of the more than 12,000 items used by traditional healers, about 500 are in common use.[5] Botanical products are used only after some kind of processing, which may include, for example, stir-frying or soaking in vinegar or wine. In clinical practice, traditional diagnosis may be followed by the prescription of a complex and often individualized remedy. Traditional Chinese medicine is still in common use in China. More than half the population regularly uses traditional remedies, with the highest prevalence of use in rural areas. About 5000 traditional remedies are available in China; they account for approximately one-fifth of the entire Chinese pharmaceutical market.[6]

Japanese TM
Many herbal remedies found their way from China into the Japanese systems of traditional healing. Herbs native to Japan were classified in the first pharmacopoeia of Japanese TM in the ninth century.[7]

Indian TM
Ayurveda is a medical system primarily practised in India that has been known for nearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind, and spirit in disease prevention and treatment.[8]

WHO GUIDELINES FOR HERBAL MEDICINES

These guidelines recognized the importance of herbal medicines to the health of many people throughout the world, stating: “A few herbal medicines have withstood scientific testing, but others are used simply for traditional reasons to protect, restore, or improve health.” Most herbal medicines still need to be studied scientifically, although the experience obtained from their traditional use over the years should not be ignored. As there is not enough evidence produced by common scientific approaches to answer questions of safety and efficacy about

| Table 1: Different WHO guidelines with their major resolutions and year of establishment |
|-------------------------------------------------|-------------------------------------------------|----------------|---|
| WHO guidelines | Major resolutions taken | Year | Ref |
| Quality control methods for medicinal plant materials | Emphasized the need to ensure the quality of medicinal plant products by using modern control techniques and include suitable standards and limits for contaminants are included. | 1996 | [7] |
| WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems | Provide technical guidance on the principles of good pharmacovigilance and the inclusion of herbal medicines in existing national drug safety monitoring systems. | 2004 | [8] |
| Guidelines for the Regulation of Herbal Medicines in the South-East Asia Region | This guideline aims to facilitate the registration and regulation of herbal medicines by establishing the foundation for a harmonized regulatory standard to meet the common demands of the region. | 2003 | [9] |
| General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine | Harmonize the use of certain accepted and important terms in TM, summarize key issues for developing methodologies for research and evaluation of TM, improve the quality and value of research in TM, and provide appropriate evaluation methods to facilitate the regulation and registration of TMs. | 2000 | [10] |
| National policy on TM and regulation of herbal medicines Report of a WHO global survey | Main objectives of this report are framing policy for safety, efficacy, and quality of herbal medicines and its promoting rational use. | 2005 | [11,12] |
| WHO guidelines on good agricultural and collection practices for medicinal plants | Quality assurance of medicinal plant materials used as the source for herbal medicines, and encourage and support the sustainable cultivation and collection of medicinal plants of good quality. | 2003 | [13] |
Table 2: Legal status of different countries for herbal drug regulation

<table>
<thead>
<tr>
<th>Country</th>
<th>Legal status/policy</th>
<th>Major responsibilities</th>
<th>Year of establishment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Therapeutic Goods Act (Commonwealth of Australia, 2001a)</td>
<td>The overall objective of the Act is to ensure the quality, safety, and efficacy of therapeutic goods, including medicines and medical devices available to the Australian public.</td>
<td>1989</td>
<td>[16,17]</td>
</tr>
<tr>
<td>Argentina</td>
<td>Health Ministry of the Provincia de Buenos Aires</td>
<td>Regulation for registration and commercialization of medicinal plants.</td>
<td>1993</td>
<td>[18]</td>
</tr>
<tr>
<td>Austria</td>
<td>Herbal medicine regulation Law No.541</td>
<td>Marketing authorizations.</td>
<td>1989</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>Belgium</td>
<td>Ministry of Health</td>
<td>Under the law, proof of quality, safety, and efficacy became an essential precondition for the registration of drugs.</td>
<td>1995</td>
<td>[21-23]</td>
</tr>
<tr>
<td>Canada</td>
<td>Natural Health Products Regulations</td>
<td>Ensure that the herbal medicinal plant product is safe under the recommended conditions of use without a prescription, effective for the proposed claims, and of high quality.</td>
<td>2004</td>
<td>[24-27]</td>
</tr>
<tr>
<td>Chile</td>
<td>Unidad de Medicina Tradicional</td>
<td>Incorporating TM with proven efficacy into health programs and of contributing to the establishment of their practice.</td>
<td>1992</td>
<td>[28]</td>
</tr>
<tr>
<td>China</td>
<td>The Drug Administration Law ofthe People’s Republic of China</td>
<td>Encourages the development of both modern and traditional drugs, protects the resources of wild herbal drugs, and promotes domestic cultivation of herbal drugs.</td>
<td>1984</td>
<td>[18]</td>
</tr>
<tr>
<td>Colombia</td>
<td>Ministry of Health</td>
<td>Issuing of license. Documentation on the manufacturing process, quality control, and, if necessary, toxicity studies.</td>
<td>1990</td>
<td>[29]</td>
</tr>
<tr>
<td>Denmark</td>
<td>Danish Ministry of Health Order No. 790</td>
<td>Proof of quality, safety, and efficacy must be given; a bibliographic application with respect to therapeutic use is accepted if it contains descriptions in the relevant scientific literature of Europe or North America.</td>
<td>1992</td>
<td>[30, 31]</td>
</tr>
<tr>
<td>Egypt</td>
<td>National Applied Research Centre for Medicinal Plants and National Organization for Drug Control and Research</td>
<td>Medical, health, and nutrient content claims made by law. Rules of GMP are implemented for herbal medicines.</td>
<td>1995</td>
<td>[18]</td>
</tr>
<tr>
<td>Estonia</td>
<td>Medicinal Products Act</td>
<td>To maintain the documents concerning chemical, pharmaceutical, biological, pharmacological-toxicological, and clinical information of the herbal drugs.</td>
<td>1996</td>
<td>[32]</td>
</tr>
<tr>
<td>Fiji</td>
<td>Pharmacy and Poisons Act of Fiji</td>
<td>Permits importation of TMs for use by ethnic communities</td>
<td>1994</td>
<td>[33,34]</td>
</tr>
<tr>
<td>France</td>
<td>French Medicines Agency</td>
<td>Marketing authorizations</td>
<td>1996</td>
<td>[36]</td>
</tr>
<tr>
<td>Germany</td>
<td>Medicines Act of 24 August 1976</td>
<td>Herbal finished drugs have to comply with the same criteria for quality, safety, and efficacy as all other finished drugs</td>
<td>1976</td>
<td>[37-39]</td>
</tr>
<tr>
<td>Greece</td>
<td>Ministry of Health</td>
<td>Issuing of license, documentation on the manufacturing process, and toxicity studies.</td>
<td>1994</td>
<td>[40]</td>
</tr>
<tr>
<td>Hungary</td>
<td>Law on Public Health, Chapter IV, Section 104</td>
<td>Herbal drugs regulated as over the counter medicines for self-medication purposes and by law, medical claims, and health claims may be made.</td>
<td>1996</td>
<td>[41]</td>
</tr>
<tr>
<td>India</td>
<td>Drugs and Cosmetics Act of 1940 and the Drugs and Cosmetics Rules of. 1945</td>
<td>Regulate the import, manufacture, distribution, and sale of drugs and cosmetics.</td>
<td>1945</td>
<td>[42]</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Directorate of Traditional Drug Control</td>
<td>Production, distribution and labeling of traditional drugs, and licensing of traditional drugs and imported traditional drugs.</td>
<td>1975</td>
<td>[18]</td>
</tr>
<tr>
<td>Ireland</td>
<td>Guidelines for Application for Product Authorization of Herbal Products* issued by National Drugs Advisory Board</td>
<td>Licensing of manufacturers and authorization of herbal products.</td>
<td>1985</td>
<td>[43,44]</td>
</tr>
<tr>
<td>Italy</td>
<td>Italian Health Authority</td>
<td>Grant licensed and ensure the quality, safety, and efficacy.</td>
<td>1981</td>
<td>[45]</td>
</tr>
<tr>
<td>Japan</td>
<td>Ministry of Health and Welfare</td>
<td>Improve quality control of Kampo drugs</td>
<td>1972</td>
<td>[46]</td>
</tr>
<tr>
<td>Korea</td>
<td>The Ministry of Public Health and Social Affairs</td>
<td>Regulate and rule on the herbal medicines and their preparations.</td>
<td>1969</td>
<td>[47-50]</td>
</tr>
<tr>
<td>Malaysia</td>
<td>National Pharmaceutical Control Bureau, Ministry of Health</td>
<td>Manufacturing, import, supply, or sailing of the TMs.</td>
<td>1968</td>
<td>[18]</td>
</tr>
<tr>
<td>Mali</td>
<td>Traditional Medicine Department under the Ministry of Health</td>
<td>Postmarketing surveillance and adverse effect monitoring of herbal medicines.</td>
<td>1968</td>
<td>[18]</td>
</tr>
</tbody>
</table>

Table 2 Contd.
The guidelines issued by WHO have resulted in the creation of 83 monographs on herbal drugs that are used either in their natural state after desiccation or concentration or for the isolation of natural active ingredients. The European Pharmacopoeia was created in 1964; its efforts have resulted in the production of 100 monographs on herbal drugs. These guidelines define the basic criteria for the evaluation of quality, safety, and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations, and manufacturers in assessing documentation, submissions, and dossiers in respect of such products.

The below mentioned WHO guidelines [Table 1] stressed the need for assessment of efficacy including the determination of pharmacological and clinical effects of the active ingredients, cultivation and collection of the medicinal plants, and labeling which includes a quantitative list of active ingredient, dosage, and contraindications.

### Table 2: Legal status of different countries for herbal drug regulation

<table>
<thead>
<tr>
<th>Country</th>
<th>Legal status/policy</th>
<th>Major responsibilities</th>
<th>Year of establishment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mongolia</td>
<td>Traditional Medicine Department under Mongolian National Medical University</td>
<td>Production, development, and investigation of TMs.</td>
<td>1989</td>
<td>[51]</td>
</tr>
<tr>
<td>Nepal</td>
<td>Department of Drug Administration under the Ministry of Health</td>
<td>Price approval, safety, efficacy, and quality of products. Authorization for import, export, and distribution of the product, and the mode of distribution and promotion.</td>
<td>1996</td>
<td>[52]</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>The national pharmaceuticals law-292</td>
<td>Safety assessment</td>
<td>1998</td>
<td>[53]</td>
</tr>
<tr>
<td>Oman</td>
<td>Ministry of Health</td>
<td>Grant of license for manufacturing and import permission</td>
<td>1995</td>
<td>[54]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>The Drugs Act of 1962</td>
<td>Controls the regulation of herbal medicines as regards advertising and prevention of misuse</td>
<td>1962</td>
<td>[18]</td>
</tr>
<tr>
<td>Portugal</td>
<td>Portugal Drug Act</td>
<td>Regulation of herbal medicines in the same laws as those covering conventional pharmaceuticals.</td>
<td>1995</td>
<td>[55]</td>
</tr>
<tr>
<td>Qatar</td>
<td>Ministry of Public Health</td>
<td>By law, medical, health, nutrient content, and structure/function claims may be made about herbal medicines.</td>
<td>1990</td>
<td>[56]</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Ministry of Health, KSA</td>
<td>Medical, health, nutrient content, and structure/function claims may be made</td>
<td>1996</td>
<td>[18]</td>
</tr>
<tr>
<td>Singapore</td>
<td>Traditional Chinese Medicine Practitioners Act</td>
<td>Marketing authorization and licensing of manufacturers.</td>
<td>2000</td>
<td>[57,58]</td>
</tr>
<tr>
<td>South Africa</td>
<td>Medicines Control Council (MCC)/ Dietary Supplement Health and Education Act</td>
<td>Safety assessment requirements include traditional use without demonstrated harmful effects, reference to documented scientific research on similar products, and clinical data.</td>
<td>1994</td>
<td>[2]</td>
</tr>
<tr>
<td>Spain</td>
<td>The Spanish Medicinal Products Act No. 25</td>
<td>Objective of the Act is to ensure the quality, safety, and efficacy of therapeutic goods, including herbal medicines. Marketing authorization. And implementation of GMP rules.</td>
<td>2002</td>
<td>[61]</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Therapeutic Products (Swissmedic) under Federal Department of Home Affairs</td>
<td>Premarking control, licensing and registration process, and postmarketing control by quality control analysis.</td>
<td>1967</td>
<td>[18]</td>
</tr>
<tr>
<td>Thailand</td>
<td>The Drug Act B.E. 2510</td>
<td>Premarking control, licensing and registration process, and postmarketing control by quality control analysis.</td>
<td>1967</td>
<td>[18]</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Medicines and Healthcare products Regulatory Agency (MHRA) and Medicines Act 1968</td>
<td>Premarking control, licensing and registration process, and postmarketing control by quality control analysis.</td>
<td>1968</td>
<td>[62-66]</td>
</tr>
<tr>
<td>United States</td>
<td>Food Drug and Cosmetics Act</td>
<td>Ensuring that a dietary supplement is safe before it is marketed, and the United States Food and Drug Administration is responsible for taking action against any unsafe dietary supplement product after it reaches the market.</td>
<td>2000</td>
<td>[67-70]</td>
</tr>
</tbody>
</table>

Most of the herbal medicines now in use, the rational use and further development of herbal medicines will be supported by further appropriate scientific studies of these products, and thus the development of criteria for such studies. In this regard, WHO has issued guidelines for the assessment of herbal medicines. These guidelines defined the basic criteria for the evaluation of quality, safety, and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations, and manufacturers in assessing documentation, submissions, and dossiers in respect of such products.

The European Union

The European Pharmacopoeia was created in 1964; its efforts have resulted in the creation of 83 monographs on herbal drugs that are used either in their natural state after desiccation or concentration or for the isolation of natural active ingredients. The Association of the European Self-Medication Industry has carried out a study for the European Commission on herbal medicinal products in the European Union (EU). The following summary is taken from this report."[8] The importance of herbal medicinal products varies from one country to another. These products are not a homogeneous group. In general, they are either fully licensed medicinal products with efficacy proven by clinical studies or by references to published scientific literature (in accordance with Article 4.8 a (ii) of Council Directive 65/65/EEC) or are available...
as products with a more or less simplified proof of efficacy according to their national use. Many Member States have these two categories, but there are major discrepancies between the Member States in the classification of individual herbal drug preparations and products into one of these categories as well as in the requirements for obtaining a marketing authorization. According to Council Directive 65/65/EEC,[15] which has been implemented in national law in all Member States, medicinal products require prior marketing approval before gaining access to the market. In almost all Member States, herbal medicinal products are considered as medicinal products and are, in principle, subject to the general regulations for medicines as laid down in the various national medicine laws. In many cases, a specific definition of herbal medicinal products is available, which is in line with the EU Guideline “Quality of Herbal Medicinal Products.” This includes plants, parts of plants, and their preparations, mostly presented with therapeutic or prophylactic claims. Different categories of medicinal products containing plant preparations exist or are in the process of being created. For instance, draft legislation in Spain includes the definitions “herbal medicinal products” and “phytomedical products.” The latter are not considered as “pharmaceutical specialties” and are therefore not classified as herbal medicinal products.

Legal status of different countries for herbal drug regulation
Legislative controls in respect of medicinal plants have not evolved around a structured control model. There are different ways in which countries define medicinal plants or herbs or products derived from them, and countries have adopted various approaches to licensing, dispensing, manufacturing, and trading to ensure their safety, quality, and efficacy, and due to these reasons herbal preparations varies from country to country. In some, phytomedicines are well established, whereas in others they are regarded as food and therapeutic claims are not allowed. This article follows a generalized template that includes regulatory authorities of various countries and their major responsibilities with year of establishment [Table 2].

CONCLUSION
The growth of the pharmaceutical industry and the unceasing development of new and more effective synthetic and biological medicinal products have not diminished the importance of medicinal plants in many societies. On the contrary, population growth in the developing world and increasing interest in the industrialized nations have greatly expanded the demand for medicinal plants themselves and the products derived from them. Regulations in countries for the assessment of the quality, safety, and efficacy of medicinal plants, and the work of WHO and EU in supporting the preparation of model guidelines in this field, have been helpful in strengthening recognition of their role in health care. It is hoped that assessment of these traditional remedies could become the basis for a future classification of herbal medicines, as well as for evaluative studies on their efficacy and safety, and their potential use in national healthcare systems in different parts of the world.

AKNOWLEDGEMENT
The authors acknowledge the University Grant Commission [F. No. 34-131/2008 (SR)], New Delhi, India, for financial support.

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69. Goldman SA, Kennedy DL. FDA’s Medical Products Reporting
How to cite this Article:
Source of Support: University Grant Commission [F. No. 34-131/2008 (SR)], New Delhi, India., Conflict of Interest: None declared

Ajazuddin and Saraf: Legal regulations of complementary and alternative medicines in different countries


Authey Quary ???