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Herbal insecticides and Acaricides: Challenges and constraints

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Abstract
In the recent scenario, more than 80% population of the world depends on herbal medicine for primary health care. The traditional or folklore medicine systems predominated in certain developed and developing countries including China, Africa, Germany, India etc. Arthropods and arthropod-borne diseases cause immense economic losses throughout the world including India. Attempt to control arthropods using synthetic insecticides and acaricides lead to widespread emergence of insecticide and acaricide resistance, their residue in the final products and undesirable persistence in the environment. To delineate these troubles, the use of herbal insecticide and acaricide is the emerging concept. These substances are widely available and have the properties of rapid degradation, non-selective nature, immuno-stimulatory activity, causing low mammalian toxicity and overall eco-friendly or environmentally beneficial in nature. Some herbal insecticide and acaricide are pyrethrum, neem and various essential oil and extracts from different plant material. These compounds act by inhibiting the growth as well as development and reproduction in various ways to control the population of flies, fleas, lice, ticks, and mites of medical and veterinary significance. The standardization and quality control of these herbal drugs is becoming a challenging task because of several drug toxicity and undesirable drug-interaction with other compounds. Harvesting procedures, short residual activities, difficulty in conducting clinical trials of the drugs due to various regulatory issues etc. and identification of bioactive components are the main constraints behind using these herbal drugs. Therefore, there is a need for proper safety and efficacy assessment, systemic pharmaco-vigilance and proper monitoring and standardization of any herbal drug before launched into the market.

Keywords: Arthropods, PDPs, pyrethrum, neem, standardization, challenges, constraints

1. Introduction

Arthropods constitute the highest living known animals on the earth (75%) as per the report of ICAR, 2012 [1]. Arthropods and arthropod-borne disease causes immense economic losses due to major threats in the health as well as production of livestock animals throughout the world including India [2]. Because of the several species of mosquitoes, tabanids flies, *Culicoides* spp., *Simulium* spp., stable fly, cattle grubs, *Haematobia irritans*, myiasis causing flies (*Calliphora*, *Lucilia*, *Chrysomia*, *Phormia*, *Sarcophaga* sp.), lice, ticks and mites infestation. Application of herbal insecticide and acaricide is the traditional or folklore practice in developed and developing countries including India since from ancient time for the control of ectoparasitic infestation. But now an alternatives or emerging field of Medical and Veterinary science where most of the insects, ticks and mites sp. develop resistance against commonly used synthetic drugs [3]. The commonly used synthetic chemicals such as chlorinated hydrocarbons, organophosphates, carbamates, formamidines, pyrethroids and macrocyclic lactones are considered as modern approaches to combat these ectoparasites. But, indiscriminate use of these chemicals leads to enhance drug toxicity, increase the emergence of widespread insecticide and acaricide resistance, a lot of drug residue in animal food products which take long time to withdrawal of active ingredients, undesirable environmental persistence and unacceptable risks to non-target organisms which influencing the normal biotic flora and fauna. Therefore, it is the time where we can change or modify our old strategies (where already insecticidal resistant become serious problems) or moving towards recent control methods for ectoparasitic infestation. Thus, one such method is the utilization of eco-friendly, safe, effective and economical indigenous plant extracts or Plant-Derived Products (PDPs) based therapy called as herbal insecticide and acaricide [4].

In the present time, the entire focus of research on plant based ectoparasiticidals is given special emphasis. So far desired effects have not been achieved in Veterinary sciences, some of the experiments, carried out using various phyto agents have shown encouraging results. If with the use of single insecticide did not satisfy the encouraging result on the insect population, then the efficacy of a single ectoparasiticidal /repellent plant can be enhanced by judicious combination with another plant or an active principle which has adjuvant properties [5]. These agents act in one or more of the following ways such as antagonists of growth regulatory hormones, anti-feedant effects, inhibition of egg development, disrupt mating and sexual communication, inhibit chitin formation and as repellants (especially for ticks). Examples of various herbal insecticide and acaricide are *Chrysanthemum* (Pyrethrum), *Cedrus deodara* (cedar oil), *Azadirachta* (Neem oil), *Cymbopogan* (Lemon grass oil), *Eucalyptus* oil (blue gum), *Citrus sinensis* (orange oil), *Syzigium aromaticum* (clove), *Mentha spicata* (spearmint), *Allium cepa* (onion), etc [6].

2. Historical importance of herbal insecticide and acaricide

Medicinal plants have been identified and used traditionally throughout the world from the beginning of human civilization [7]. It is believed that the Chinese crushed chrysanthemum plants and used the powder as an insecticide as early as 1000 B.C. [8]. The earliest record reference for using natural substance was that of Marco Polo in 1300 A.D. mentioning the use of oil for controlling mange in camels. Later on, pyrethrins were identified as the potent chemical in the Chrysanthemum plants responsible for the insecticidal properties in the crushed flowers around 1800 in Asia and a lot of extraction on different plant material done in 20th century. In Ayurveda, the famous traditional medicine systems in India where about 2000 plant species have been used successfully**.** The classical example is that of *Azadirachta indica* (Neem)- the miracle herb which has been used in folklore medicine way back, but scientifically the use as a source of natural insecticide and acaricide was discovered approximately only 26 years ago [9].

3. Current trend in herbal medicine

Herbal medicine is becoming ever more popular in today's world as people seek out natural remedies [10]. In recent scenario, out of the total population of the world, more than 80% are dependent on herbal medicine and its products for primary health care. Herbal medicine is widely used in India since ancient times particularly in rural areas, where 66.46% of the country's population lives as they have understood the test of time for their safety, efficacy, cultural acceptability and lesser side effects. Therefore, proved the natural plants are a promising source of herbal formulation [11].

Today herbal global market is estimated approximately US $ 60 billion, which is growing @ 7-12% annually and expected to be about US $ 5 trillion by 2050 [12]. In contrast to India, herbal industry worth around Rs16, 000 crores account for 8% of global biodiversity, with around 49,000 plant species of which 5,150 species are endemic [13]. The contribution of Indian herbal products in the world is less than 2% which doesn't justify the one of the such kind of rich mega biodiversity (17th) in the world and traditional knowledge our country possesses [14].

4. Ideal characters of herbal insecticide and acaricide

It should be cheap, easily available, selective, biodegradable or renewable and causes low mammalian toxicity [15, 16]. Till now there is no report of the development of resistance and are effective even against insecticide- resistant strains as there is usually a mixture of different active agents with different mechanisms of action [17, 18]. With the use of these compounds, there is a negligible drug residue in the processed product (*i.e.* meat, milk). Therefore, it should have high consumer demand on food safety aspects. It helps in the prevention of certain diseases and conserves health in humans (Malaria, dengue fever, Lyme diseases, bubonic plague, west Nile fever, yellow and dengue fever etc). Products based on the use of phyto-insecticide are preferred for exports and obtain premium price. Therefore, overall leads to environment beneficial or eco-friendly in nature *i.e.* safe for man, mammals, fishes, bird and other living creatures [19].

5. Herbal drug preparation

Ideally fresh plant parts should be collected as far as possible. The cleaning is done to remove adhered impurities followed by shed drying [20]. The accepted moisture percentage ranges from 10 to 12%. The extraction of active ingredients can be done with the help of different solvent material like alcohol, chloroform, diethyl ether, ethyl acetate etc. If the phyto-constituents are heat-sensitive, extraction methods that do not require heat are used such as cold maceration and percolation. For heat-stable constituents, decoction and Soxhlet extraction are performed [21]. Along with these methods, sonication and supercritical fluid extraction (SFE) using CO_2 as extracting fluid can also be used followed by filtration and concentration process. Qualitative phytochemical screening is carried out to investigate the different classes of active ingredients present in the extract. Such as tannins, glycosides, essential oils, flavonoids, alkaloids, ester, fatty acids etc. with the help of various biochemical tests [22]. Plant extracts contain various types of bioactive compounds having different polarities their separation still remains a big challenge for the process of identification and characterization of bioactive compounds [23]. The isolation of bioactive compounds done by using different chromatographic techniques such as HPLC, TLC, paper, column, and gas chromatography to obtain pure compounds.

6. Natural herbal insecticides

6.1. Pyrethrum

Pyrethrum is one of the oldest and safest natural insecticides used in the world today as it selectively targets insects rather than mammals due to higher insect nerve sensitivity, smaller insect body size, lower mammalian skin absorption, and more efficient mammalian hepatic metabolism. Chemically it is the mixture of several esters called pyrethrins which are extracted from the flower of *Chrysanthenum cinerariaefolium* and widely used for the control of insects as well as acarines (ticks and mites) of veterinary importance [24, 25]. Pyrethrins are gradually replaced by synthetic organophosphates and organo chlorides as the insecticides of choice as these compounds have been shown to have significant and persistent toxic effects to animal and human being. Being biodegradable in nature, pyrethrins are widely preferred to pyrethroids, which are synthetic analogues of pyrethrin that accumulate in the environment. Pyrethrins target the sodium ion channels in the nerve cells of insects and serve as neurotoxin leading to knock down effect resulting in repeated and extended nerve firings. This hyperexcitation causes the death of the insect due to loss

of motor coordination and paralysis [26]. Resistance to pyrethrin has been bypassed by pairing the insecticide with synthetic synergists such as piperonyl butoxide (PBO). The activities of these compounds together prevent detoxification in the insect, ensuring insect death. Synergistic mechanisms of these drugs make pyrethrin more effective, allowing lower doses to be effective.

6.2. Neem

Azadirachtin is the most biologically active principle found in the neem (*Azadirachta indica*). It is structurally similar to the insect hormones known as "ecdysones" which are responsible for metamorphosis in insects leading to anti-feedant effects [27]. The important properties of neem are acting as free radical scavenger due to the rich source of antioxidant and immunomodulation. Because some of the fly larvae down regulating the host's immune system which may help the parasites to avoid detection, causing suppressed eosinophil and IgG counts in the blood test [28]. All parts of neem- leaves, seeds, bark and other formulations of the neem have potent activity against the ecto-endo parasitic infection [29, 30]. Certain neem based-products such as Tresan®, MiteStop®, Wash Away Louse®, Licenser®) and other formulations were found highly effective against a wide range of veterinary and medical pests, such as dust mites, ticks, red mite of poultry (*Dermanyssus gallinae*), scabies mites (*Sarcoptes scabiei*) and head lice (*Pediculus humanus capitis*) etc [31-35]. Recently, neem bark extracts showed the property of analgesic activity and also to cure high fever as of malaria [36].

6.3. Essential oils and plant extracts:

The potential use of both essential oils and plants extracts against a wide range of economically important ectoparasites of veterinary significance [37, 38]. Various lice species have also received interest as targets for essential oils and extracts [39, 40]. Recently, essential oil has insecticidal potential focusing towards on key target groups, particularly mosquitoes toward the Integrated Mosquito Management (IMM) approach [41-43] and *Dermanyssus gallinae*, the red mite of poultry [44, 4]. The researcher needs to be attentive towards control and management of several myiasis causing flies such as *Calliphora*, *Lucilia*, *Chrysomia*, *Phormia* and *Sarcophaga* sp. by assessing the activity of various essential oils and plants extracts.

Herbal acaricidal are widely used against ectoparasites abroad and also in India. There are several plants are being used for the treatment and control of mite infection in animals [45-47]. Recently, assessed *in vitro* activity of several essential oils against *Sarcoptes scabiei* and found that 1% clove and palmarosa oil killed all the mites within 20 and 50 min, respectively [48]. A lot of studied reviewed by different worker on the use of plant material effective against ticks [15, 29, 49-56]. Recently, the profound anti-tick activity of the herbal acaricide product containing Neem oil, Karanj oil, Eucalyptus oil, Rohit Gawash and Karpura against egg and adult stages of *Rhipicephalus* (*Boophilus*) *microplus* ticks showing that treated females laid eggs very meager in number and amongst them very few have hatched [57]. Inspite of the above studies, the field is still in nascent stages and still more research needs to be done in the area to explore more and more plants products aiming to develop a low-cost, effective and potent acaricide with little or no side effect [Table 1].

7. Challenges in herbal insecticide and acaricides

The key challenges of herbal insecticide and acaricide are as follows:

7.1. Standardization and quality control: Standardization and quality control of herbal drugs are much complex because it is based on the evaluation of identity, purity and quality of the active herbal ingredients [68]. The major challenges in the development of these drugs are to control the quality of herbal drugs including safety, efficacy, toxicity and their interactions [69]. The correct identity of the cured herbal material is of prime importance in establishing the quality control of herbal drugs. To assess the identity and purity based on criteria such as type of preparation, sensory properties, physical constants, adulteration, contaminants, moisture, ash content and solvent residues have to be checked [70].

7.2. Adverse drug interactions: There are several herbal drugs which interact with other compounds leading to the harmful effects on the host body [71]. Since, all herbal medicines are complex mixtures of one or more active ingredient, multitude of active ingredients will increase the possibilities of interaction between herbal medicines and conventional drugs. Example- piperonyl butoxide (PBO) also act as synergistic which potentiate the toxicity of several natural pyrethrum and synthetic pyrethroids compounds [72].

7.3. Problems in pharmacological, toxicological and clinical documentation: There is difficulty in assessing certain pharmacological parameters such as pharmokinetics, pharmacodynamics and toxicological effects of any herbal preparation. The clinical documentation is a much more complex process involving several applications filling and verification protocols which required proper monitoring from different authorities. Thus, it is a too lengthy process which can take 5-9 years or more up to the final documentation of any drugs [73]. Finally, the post-market surveillance of drugs should be conducted studies regarding drug residue and environment, animal and human safety study concern associated with drugs.

7.4. Challenges of the clinical trial as well as the regulatory issues: There are certain loop holes in the clinical trials of herbal drugs as the lack of stringent bylaws and regulations. Hence, a deep insight of important challenges and major regulatory guidelines for clinical trial of herbal drugs is needed [74]. The quality and efficacy of the compounds used in any clinical trial should be assessed in respect of uniformity i.e. these parameters should be uniform from batch to batch. Since the quality control of these herbal insecticide and acaricides are much more complex and difficult, the relevant and appropriate guidelines should be established for the assessment of safety and efficacy for different categorized herbal medicines to reduce cost and expenditure. And, efforts should be made for the integration of traditional medicine into national healthcare systems [75].

Table 1: Selected plants derived products (PDPs) and their use against insects and acarines of Medical and Veterinary significance

Plants and its source	Bioactive ingredients	Mode of action	Indication	Available product	References
Pyrethrum (*Chrysanthemum cinerariaefolium*)	Pyrethrins, Cinerins, Jamolins	Pyrethrum compounds mainly attack sodium /potassium channels and serve as a neurotoxin lead to knock down effects.	insects, mites, scabies	Defender® Nature's way®	[24,58]
Neem (*Azadirachta indica*)	Azadirachtin Salanin, Nimbin	Neem targets the cholinergic system in insects through inhibition of acetyl cholinesterase (AchE-EC). It also exerts an anti-mitotic (G2/M phase of cell division) effect by disrupting tubulin polymerization. Also acts as feeding deterrence and disruption to growth, though oviposition deterrence, repellence, reduced fitness and sterility by toxicants activity.	Insects, ticks, mites, lice, fleas etc.	Margosom®, Tre-san®, MiteStop®, LouseStop®, Licener®, Azera™ NeemAzal®, Nimex,	[27, 28, 36, 57, 59-62]
Essential oil and plants extracts	Terpenes, various plants extracts	Larvicide, insect's growth regulators, repellent, toxicants and disruption of transient receptor potential channels.	Mosquitoes, other insects & acarines.	Breck-a Sol®, Mediker®, Tea Tree Gel®	[37-57]
Safflower (*Carthamus tinctorius*)	Serotonin, glucopyranoside	Anti-inflammatory, anti-oxidants effect & dermatological effects by inhibition of tyrosinase activity.	Psoroptic mange	-	[63]
Cedar wood (*Cedrus deodara*)	d- Limonene	Repels insects and other microorganisms especially mosquitoes.	Mosquitoes, mite etc.	-	[64]
Haldi (*Curcuma longa*)	Curcumin	Powerful anti-inflammatory and strong antioxidant effects.	Ticks, mites	-	[65,66]
Karanj (*Pongamia pinnata*)	karanjin, debitterised karanjin oil	Feeding deterrent, repellent, growth regulator, oviposition suppressant or sterilant.	Insects	Derisom ®	[67]
Tabacco (*Nicotiana tabacum*)	Nicotine, Solanine	It competes with AchR, at nerve synapses and causing uncontrolled nerve firing results in rapid failure of those body systems.	Insects, mites etc.	Nico Dust	
Garlic (*Allium sativum*)	Sulphur Compounds	Miticidal and act as non-toxic repellents.	Various Insects	AjoNey, EcoA-Z ®	
Chile/Pepper (*Capsicum annum*)	Capsaicin	Metabolic disruption, membrane damage and nervous system failure, repellent action.	Insects	Hot Pepper Wax, ChileNey	
Custard apple (*Annona squamosa*)	Squamocin (annonin),	Both insecticidal and fungicidal activity by inhibiting mitochondrial Complex III.	Scabies mites, ticks	Anosom ®	
Burmese (*Derris elliptica*)	Rotenone	Inhibitor of cellular respiration (mitochondrial complex electron transport inhibitor).	Insects, mites etc.	5.0% Rotenone ME,	

7.5. Safety and Efficacy Assessment in Herbal Drugs: The major difference in the assessment of quality, safety and efficacy would hinder the free circulation of herbal medicinal products may represent a risk for consumers [76]. This need should be vigilant when using herbal remedies, particularly in specific conditions (pregnancy and pediatric population) [77]. Increasing the use of nutraceutical (herbal nutritional) products such as prebiotic, probiotic and adoptogens in the today diversified marketing [78]. Application of synchronize multi-laboratory demonstration analytical methods and transparency in supply chain through vendor-audits are the other requirements for quality assurance of these drugs [79]. There is certain lack of scientific operating processors (SOP) evidence to evaluate safety and efficacy of herbal drugs [80].

7.6. Safety, Monitoring and Pharmaco-Vigilance: The safety of herbal drugs has become an issue for the regulatory authorities, as certain serious effects have been reported while using these compounds including several hepatotoxicity (*Lantana camara*, *Hypericum perforatum*, *Senecio*, *Crotolaria* etc.) and renal failure (*Datura stromonium*, castor oil, *Amaranthus retroflexus* etc.) [81]. Recently, in 2014, the Government of India established a separate department-AYUSH under the Ministry of Health and Family Welfare for monitoring activity related to herbs and its product. To promote health related issues systemic pharmaco-vigilance is necessary. For this purpose, WHO (1998) [82] put forward several guidelines for quality control of herbal drugs such as ensuring the stability and shelf life of any products and also ensuring quality of raw material and the final product (in manner of LD_{50}/ED_{50}). Quality and safety parameter should also be assessed in reference to any contaminants and pesticide residue in herbal drugs.

7.8. Intellectual Property Rights (IPRs): IPRs is to prevent the copying or being stolen through getting diverse forms of right from the authorities. Since the different rights are granted by the national government for the betterment of human life styles from the use of thought or intellects. Therefore, documentation of folk knowledge thus important for our future rights [83].

8. Constraints in herbal insecticide/acaricides

The primary constraints like indiscriminate pre and poor post-harvesting practices of herbal drugs. There is a lot of chemical variabilities has been reported between essential oils from different varieties, area to area, season, type of extraction etc. For the identification of individual bioactive ingredients: The technical grading parameters should be fixed by different manufacturers for neem, terpenes (thymol), eugenol etc. [84].
These compound having short residual activity. Therefore, it requires a dose of the same crude drug even after a certain period to maintain the minimal inhibitory concentration (MIC) of those particular drugs [30, 85]. Various type of toxicity associated with these compounds due to complex drug-interactions [86]. The onset of action is slow or these

compounds having variable efficacy [54]. Sometimes, rapid knock-down cannot be assumed universal for certain PDPs except pyrethrum, essential oils and terpenes [15, 87]. Lesser half-lives of the most essential oil based products and rapid degradability of active ingredients leading to minimal effects on non-target organisms.

There is lack of reliability and residuality and non-target toxicity because of insufficiency of standard operating processors (SOP). There is difficulty in marketing due to lack of access to the latest technological, market information, trained personnel and equipment and constraints with clinical trials due to regulatory issues. Prolonged use of these PDPs may raise new issues regarding their environmental toxicity. Hence, short persistence times may even be considered advantageous. Toxicity, high cost and lack of efficacy data are the other culprits.

9. Future perspective and conclusion

With the judicial use of ancient knowledge of Herbalism, Ayurveda, and utilization of bio-resources along with medical science leading to the transformation of current principles towards herbal medicine, phyto-pharmaceuticals, nutraceuticals (plants used in diet supplements to prevent disease e.g. fortified feed, Vit-E & K and Selenium preparations) and cosmoceuticals (plants product to enhance the health as well as beuty purpose) can help in better servility, economy and giving employment to the marginal farmers [4].

A long list of potentially insecticide and acaricide exists in modern days and will continue to grow in the coming future. However, in order to harness these herbal products should work to their full target potential. There are several avenues that have to be explored further considering modes of action (of containing active ingredients) and their metabolism. In recent days one of the common research question along with the use of these natural herbal drugs are still viewed by several workers as xenobiotics, thus having similar targets and metabolic pathways to synthetics.

While using herbal insecticide/acaricide, environmental safety is of primary importance. So that the drug does not causing any undesirable persistence in the environment, should be of negligible resistance and residue in the final product and free from any type of toxicity. With the help of proper standard technique, drugs should be assessed properly before coming into the market. There should be need of collaborative research by comparing the efficacy of different plants material in the same insect's species repeatedly. So, by this way, we have to know about the content of any plant material in respect of any challenges and constraints. Currently, there is a need of molecular farming for the production of biopharmaceuticals and edible vaccines in plants which is a future approach to combat these ectoparasitic infestations [88].

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