

HERBAL TRANQUILLIZERS AND THEIR USES IN VETERINARY PRACTICE

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Tranquillizers are agents that decrease anxiety, fear and aggression in animal species. They exert quietening and calming effect in animals. They are used in veterinary practice to quieten the apprehensive animals, as anaesthetic premedicant, behavioural modifier and anti stress agent and galactagogue especially in psychologically disturbed animals. According to Zhang (2004) Herbal remedies that have demonstrable psychotherapeutic activities have provided a potential to psychiatric pharmaceuticals and deserve increased attention in future studies.

History

Herbal tranquillizers may be one of the oldest ethnic medicines used by human beings. In good old days when there was no analgesics or anodynes available, people used these plants to get symptomatic relief from pain. *Amanita muscaria* (the common Fly Agaric) is often regarded as the first psychoactive drug obtained from nature with modern theories positing the discovery of its psychoactive properties since 10,000 BC. Opiates, obtained from poppy plant (*Papaver somniferum*) are thought to be the first drug that is used by human beings as tranquillizer. As per the evidences available, it was used by human beings long back as 879BC. It was followed by Ganja (*Cannabis indicum*), which dates back to the Bible age. The Hebrew Bible mentions it in Exodus 30:23 where God commands Moses to make a holy oil of myrrh, cinnamon, cannabis (*qinçh bouem*) and cassia to anoint the Ark of the Covenant and the Tabernacle (and thus God's Temple in Jerusalem). Later some plants like Indian snake root

(*Rauwolfia serpentina*) were also discovered. Almost all the ethnic medical systems, such as Greek, Arabic, Chinese and Oriental systems of medicines used these plants as a part of their prescription. Even now, modern medicine, Ayurveda, and Siddha systems use them as medicines in varied disease conditions, such as behavioural modifiers and to alleviate pain in painful conditions. While the modern medicine uses the active chemicals isolated from the plants in its pure form or its synthetic derivatives or analogues, the other systems use the active plant as such or its decoctions or extracts for the purpose. In Veterinary practice phyto tranquillizers are used as antistress, adaptogenic and galactagogue.

Mechanisms of tranquillization.

There are so many plants in nature that are found to possess central nervous system depressant property. Neither the active chemical ingredient nor the

mechanism by which it produces tranquillization is fully elucidated. There are two types of neurotransmission in brain, excitatory and inhibitory. The major receptor groups in the brain are

(a) Dopamine receptors

There are five dopamine receptors in the body designated as D1 to D5. D1 and D5 are excitatory by virtue of their ability to increase the intracellular cAMP level whereas D2, D3 and D4 are inhibitory as they reduce the level of intracellular cAMP level.

(b) Adrenergic receptors.

There are two types of adrenergic receptors in the body. Alpha(a) and Beta(b), of which alpha is the predominant one in the brain. There are two types of alpha receptors in brain α_1 and α_2 . α_1 stimulation produces CNS excitation while α_2 produces inhibition of α_1 and thus producing a CNS depressant property, the classical example being Xylazine.

(c) 5-Hydroxy Tryptamine receptors

5-HT or serotonergic receptors are one of the major inhibitory neurotransmitters in brain. There are many receptor subtypes 5-HT₁₋₇ which are again subdivided into many groups. In them, 5-HT_{1A} and 5-HT_{1B} are responsible for CNS depression, 5-HT_{2A}, 5-HT₃ and 5-HT₄ causes CNS excitation, 5-HT_{2A} stimulation produces emesis and 5-HT₁₀ affects locomotion. In general if either the excitatory is suppressed or the inhibitory receptor is stimulated, it can produce tranquillization.

(d) γ -aminobutyric acid (GABA) receptor.

Along with glycine receptor that is predominantly found in spinal cord, GABA forms the most important inhibitory neurotransmitter in brain as 20-50% of all central synapses are equipped with GABA. There are 3 subtypes, viz A, B and C, among which A forms the most important CNS depressant.

(e) Benzodiazepine (BDZ) receptors

These receptors are actually an integral part of GABA receptors and seen in abundance at ascending reticular formation (the area in brain which maintains wakefulness) and limbic system (the area which controls behaviour). Any ligand which can stimulate these inhibitory receptor will produce tranquillization.

So these are the proposed sites of activity of herbal tranquillizers. The basic mechanism of action of the active ingredients may be broadly

catagorized as

1. Depression of excitatory receptors/neural circuits of brain. (Dopamine receptors, Adrenergic receptors etc.)
2. Stimulation of inhibitory receptors/ neural circuits of brain.(5-HT receptors, benzodiazepine receptors, GABA receptors)

All the herbal tranquilizers are also thought to act through any of these pathways. It has been experimentally proven that many herbals are found to possess active chemical ligands that are capable of binding to the above receptors in brain. Kaneko *et al.*(2005) reported that Hange-koboku-to, a Kampo (Japanese traditional medicine system) medicine, modulates cerebral levels of 5-HT (5-hydroxytryptamine), NA (noradrenaline) and DA (dopamine) in mice. Huen *et al.*(2003) reported that 5,7-Dihydroxy-6-methoxy flavone, a benzodiazepine site ligand was isolated from *Scutellaria baicalensis* Georgi, with selective benzodiazepine receptor antagonistic properties. Lin *et al.*(2003) found out that The anxiolytic mechanisms of alcoholic extract of ting-chih-wan, chinese herbal medicine might be due to decreased catecholaminergic activity caused by the increase in the turnover rate of catecholamines in the brain and decreased concentrations of 5-HT in the brain stem via activating somatodendritic 5-HT_{1A} auto receptors and inhibiting postsynaptic 5-HT receptors. Mizovaki *et al.*(2001) suggested that anxiolytic property of Kami-Shoyo-San (TJ-24), a Chinese herbal medicine may be due to a neurosteroid synthesis followed by GABA(A) / BDZ receptor stimulations. All these findings suggest that the plants that are found to possess a tranquilizing property may contain an active ingredient, which can bind to one or more of the above mentioned receptors.

2. Mechanism of galactagogue action of tranquilizers.

Perhaps this will be the most common use of herbal tranquilizers in Veterinary practice. There are more than one mechanisms by which they enhance milk production.

1. Milk production by lactotrophic cells in the udder is regulated by prolactin, a hormone secreted by pituitary gland, under the influence of another inhibitory hormone called prolactin inhibitory factor (PIF). This PIF is chemically dopamine. So those tranquilizers possess a property of dopaminergic inhibition can act as galactagogues, as they increase the prolactin level which in turn increase milk production.
2. Stress, fear and anxiety can reduce milk production by virtue of increased corticosteroidal and adrenergic activity. Adrenaline will suppress oxytocin activity. There are many plants in India, that are found to have central nervous system depressant property. Examples are *Nardostachys jatamansi*, *Acorus calamus*, *Leptadenia reticulata*, *Clitoria ternatea*, etc are commonly used as tranquilizers. Many proprietary Ayurvedic Veterinary formulation viz Leptaden, Milkoplex plus etc contain one or more herbal tranquilizer extracts. Traditional Japanese

medical system (Kampo) also uses herbal preparations that have CNS depressant properties. (Toriizuka *et al*, 2005.).

Toxicity

Many people consider that the drugs derived from plant origin or the whole plant or its extracts are safe and will not produce any toxic effects in the body. But on the contrary many findings suggest that it is not so. Brauer *et al* (2003) found out that a herbal tranquilizer, *Piper methysticum* can produce acute liver failure. Ryu *et al*(1998) reported Genotoxicity of *bojungchisup-tang*, an oriental herbal decoction-in *in vitro* chromosome aberration assay. Strahl *et al* (1998) mentioned about necrotizing hepatitis after taking herbal remedies in human beings. So before using them as a clinical remedy various toxicological evaluations must be done. Many herbal products may be available as over-the counter drugs, but, the availability of herbal products as "over-the-counter" drugs and their increasing usage have caused concern, since these products are not currently monitored for their safety, efficacy and quality. Reliable information on these aspects of the products is not available. However, further and large-scale, well-designed clinical investigations are needed to establish their efficacy before they can enter the mainstream drug market Most of the clinical trials carried out to date have been lacking in scientific design, data collection and interpretation, and systematic toxicological evaluation. (Kaul and Joshi,2001.).

So, as any other treatment methods, the Veterinarian should also familiarize themselves with the knowledge of indigenous drugs. Balancing traditional therapies with requests for herbal remedies is a common challenge for physicians. The most successful intervention occurs when doctors familiarize themselves with herbal preparations and educate clients about the treatments. (Rhodes-Kropf *et al*, 2001). According to Dhawan *et al* (2002), the herbal pharmacopoeias, which are still in their "infancy," can be strengthened by incorporating the appropriate bioactive constituents that need to be identified by using modern technological procedures. Once the appropriate bioactive constituent(s) are established and authenticated, their qualitative and quantitative assay procedures can be developed. Reporting the vital fingerprint parameters of the plant and incorporation of assay procedures of the bioactive phytomoiety in the official monographs of medicinal plants will certainly strengthen the herbal pharmacopoeias. This is perhaps the most important scientific approach that would ensure uniform standards and bioequivalence of plant-medicines - a need to revive faith in the healing potentials of plant-derived medicines. This is especially applicable with herbal tranquilizers also, as they affect the most vital part of the body, the brain.



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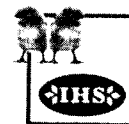


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