

Role of Phytochemicals in Lumpy Virus Skin Disease.

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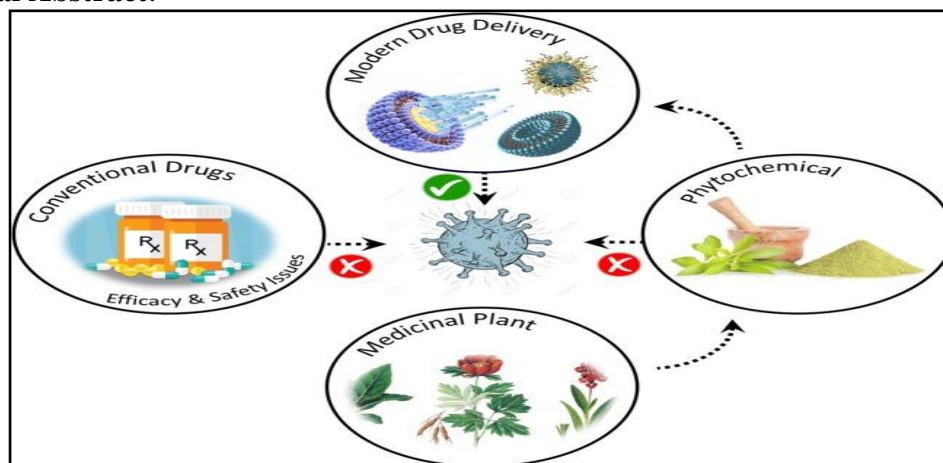
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Abstract:

Lumpy skin disease, which is caused by lumpy skin disease virus, is among the major health problems affecting the livestock industry of most African countries. Skin lesions are the major sources of infection; although the virus is evacuated via different body secretions and excretions including semen. Thus, susceptible hosts contract the virus principally by mechanical means from hematophagous arthropods, including biting flies, mosquitoes and ticks. Transstadial and transovarial persistence in various species of ticks is also possible. Following infection, characteristic lumpy skin disease lesions may explode from 7 to 14 days post infection under experimental conditions whereas in natural cases it takes 2 to 5 weeks. A pronounced socio-economic collapse is driven by reduced quantity and quality of milk, udder infection, thinness, low quality hides, loss of draught power, abortion, infertility, limitation to meat ingestion, higher morbidity, etc. Animals of any age and gender are susceptible to the disease. The morbidity rate varies according to the immune status of animals and frequency of mechanical vectors. Lumpy skin disease is manifested by distinguishing firm, circumscribed, few (mild forms) to multiple (severe forms) skin nodules, which sometimes involve mucous membranes of respiratory system, urogenital system and other internal organs. Subsequently, milk production lessens, abortion, temporary or permanent sterility, damage to hide and deaths will occur which further contribute to a momentous economic loss in cattle producing countries. Therefore, large-scale vaccination combined with other appropriate control measures are the most effective way of limiting the spread and economic impact due to lumpy skin disease. This review is designed with the aim of providing, latest information on the biology of lumpy skin disease virus, mechanism of spread, clinical and pathological features & role of Phytochemicals of lumpy skin disease.

Keywords: History, Clinical signs, LSD, LSDV, Lesions, Pathogenesis, Transmissions, Prevention, Treatment, Role of phytochemicals.

Graphical Abstract:



Introduction:-

Lumpy skin disease (LSD) affects livestock breeding like Buffalo, cows, etc (except sheep and goats). It can affect all ages and all other kinds of breed livestock. Lumpy skin disease can cause nodes on the skin, fever or may lead to the death of animals. The nodes are well restrict, round, slightly raised firm and painful.^[1,2] The mucosa of GI tract, difficult in breeding due to respiratory tract are infected. It also affect in genital tract. It can be transmitted by blood-feeding insects like mosquitoes, biting insects, etc. It incubated time period is around 4- 14 days .So that the World Organization of Health (OIE) has placed on notifiable disease list is due significant economic losses and potential for rapid spread.^[2,3] It affects economical of the animal industry like milk, milk products, the leather industry and meat production, etc. It can also affect the condition of animal, infertility rate, abortion and damage hides. It affect mortality rate in naïve population up to 5% where as morbidity rate vary from 3% -85%. In India the morbidity rate is 7%.^[4,5]

It is similar to sheep pox (SPPV) and goat pox (GTPV) of the genus capripoxvirus family Poxviridae. It double standard DNA which encloses by a lipid envelope. Its size is around 230nm - 260nm and Its weight is 150 kilobase pairs. In Initial stage the fever may exceed around 1-3 day . And the nodes is started Within 1-4 day. In 2-3 week, the nodules either regress or necrosis of the skin which results in harding, rise areas clearly separated from the skin. Sometimes it leave the large hole on the skin which may infected by bacteria infection or viral infection.^[5]

It originates from the African continent the first case was found in Zambia country. So lately it spread to countries north Africa, middle east, Europe and in asia.^[5] In India the case were report around 2,400,000+ and around 100,000+ animal were death. And on 21 September 2022, in Rajasthan was report case around 65% and death where report more than 40,000. In India the first case was reported in august 2019. It increases the number of cases of covid-19 due to crippling sanctions in endemic regions, as well as an increase in the legal and illegal trade of live animals and animal products, and also global climate change.^[6] Some herbal drugs like black pepper (disinfectants), salvia officinalis (Anti-inflammatory), Emelia ribes(Anthelmintic), piper betel (antiseptic), and many more do not work directly but reduce the effect.^[7,8]

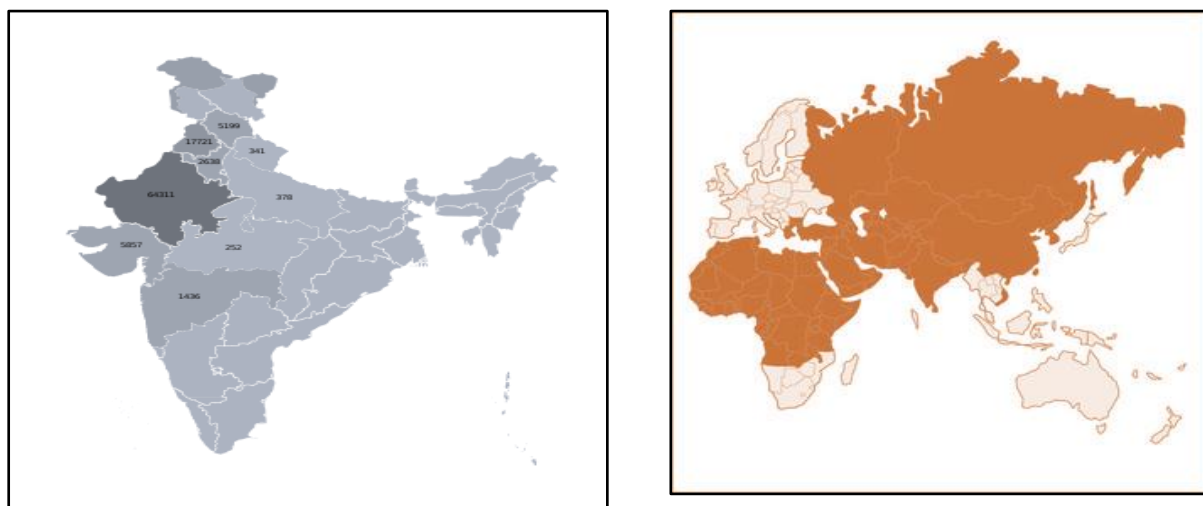


Figure No. 1- Geographical distribution of LSDV cases in India & South Africa

History:

The first case was found in Zambia in 1929 . Then it spread to Botswana and south Africa in 1943 and 1949. So afterward the it spread throughout the other part of African countries in 1950 and 1980.^[5]In April 2009 , a severe disease of cattle resembling LSD was reported from Nezwa (interior) , Alqabel (eastern) , sohar,saham(batinah) and burimi region.The

outbreaks involved seven herds (64 north oman, jersey and cross-bred cattle) and one herd (3300 holstein-friesian dairy cows) at NEZWA and sohar , respectively. Samples are collected from 22 and 38 cows from nezwa and sohar respectively. Basically skin biopsies were collected for virus isolation , negavtive staining , and polymerase chain reaction (PCR) for transmission electron microscopy and histopathology . sera was collected for serum neutralization testing and necropsies were performed on two dead Holstein-friesian animals.^[9]

Origin and spread:-

The lumpy skin disease, sheep pox virus and goat pox virus are having same genous (capripoxvirus). The species of capripoxviruses was can be spread through it . The genes sequence of three members are found it and their average size is about 150kb and encode between 147 and 156 putative genes. The genomicanalysis suggests that based of close similarity among the member of the capripoxviruse. The lumpy skin disease virus gene was similar to the goatpox virus and sheeppox virus. The sheepox virus was originally described in the 1st century AD and goatpox virus was found in northen Africa and southern Europe in 1880s.^[10] The lumpy virus was spread through special kind of flies, mosquitoes or ticks.^[11]

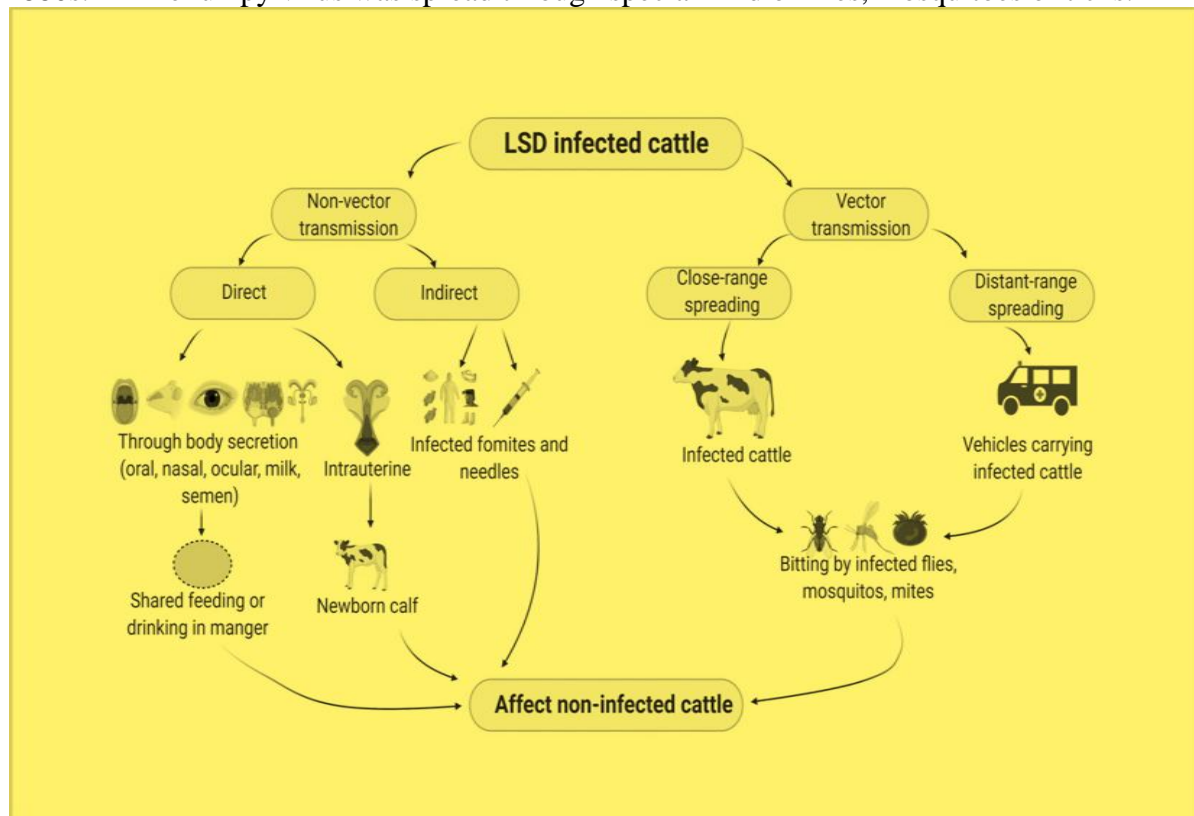


Figure No. 2- Epidemiology of Lumpy skin disease

Epidemiology of Lumpy skin disease in cattle:

The causal virus is related to that of sheepox. It is disease basically appears epidemically or sporadically. Frequently, new foci of infection appear in areas far removed from the initial outbreak. The existence of a specific reservoir for the virus is not known, nor is how and where the virus survives between epidemics. Its incidence is highest in wet summer weather, but it may occur in winter.^[21] It is most prevent along water courses and on low ground . Because quarantine restriction designed to limit the spread of infection often fail,biting insects have been suspected as mechanical vectors; however outbreaks have occurred under conditions in which insects practically could excluded .The morbidity (10-20%) is high and mortality is very low (1-5%) .^[12]

Clinical features of lumpy skin disease in cattle :-

Infected cattle develop fever, lacrimation, nasal discharge, and hyper-salivation, followed by the characteristic eruption on the skin and other parts of the body in 50% of susceptible cattle. The incubation period of disease varies from 1 to 4 weeks and then develop fever and after viral entry, which continues about 4-14 days.

The skin nodules (10-50 mm diameter) or it may vary and these sub acute or apparent. They are well circumscribed, round, slightly raised, firm, painful and involve the entire cutis and the mucosa of the GI, respiratory, and genital tracts. Additional clinical signs comprise lacrimation and nasal expulsion, enlarged subscapular and pre-femoral lymph nodes, and reduced milk yield. While abortion, prolonged fever, emaciation, and lameness may occur in infected animals. Swollen skin nodules may separate from the healthy skin and dry and harden to form a "sit-fast". Secondary bacterial infections may occur. Rhinitis and conjunctivitis can also be seen. Lameness may result from inflammation and edema of the legs, and abortion and sterility may occur in both bulls and cows. [13]



Figure No. 3- : Illustrative clinical feature of LSD.

Economic Impact:

Lumpy skin disease has led to serious economic losses in affected developed as well as developing countries. The disease causes a considerable reduction in milk yield (from 10% to 85%) due to high fever and secondary mastitis. Other consequences of the disease include damaged hides, decline of the growth rate in beef cattle, temporary or permanent infertility, abortion, treatment and vaccination costs and death of infected animals. Total production losses resulting from the disease have been estimated at 45%–65% in industrial cattle farming. Therefore, accurate and timely diagnosis in endemic areas, vaccination with the homologous strain of the LSDV, vector control, animal movement restriction (cattle fairs) and LSDV testing of bulls used for breeding are highly recommended as tools to control further spread. It is imperative to find early treatment and vaccine for the prevention of nodular skin disease (LSD), only then we can bring an emerging infectious disease in cattle under control. We can also cure Lumpy skin disease (LSD) with herbal treatment there is some evidence of this in research of treatment of capriovirus.

Diagnosis:

Most important diagnosis is by histopathology, virus isolation, or PCR. The disease may be confused with the less clinically important pseudo-lumpy skin disease, which is caused by herpesvirus (bovine herpesvirus -2). It is the same as a clinical disease so it is called as bovine herpes mammillitis. *Dermatophilus congolensis* also causes skin nodules in cattle.

LSD signs range from inapparent to severe disease. There is no current evidence of variations in virulence regarding the different LSDV strains

- 1] Fever that may exceed 41 degree Celsius.
- 2] Marked reduction in milk yield in lactating cattle.

3]Depressions, anorexia and emaciation.

4]Rhinitis , conjunctivitis and excessive salivation .



5]Recovery from sever infection is slow due to emaciation , secondary pneumonia,mastitis,and necrotic skin plugs,which are subject to fly strike and shed leaving deep holes in the hide.







Differential Diagnosis:-





Severe LSD is highly characteristic, but milder forms can be confused with the following :



- Bovine popular stomatitis (parapoxvirus)
- Demodicosis
- Insect or tick bites
- Dermatophilosis
- Vaccinia virus and Cowpox virus
- Rinderpes
- Urticaria
- Onchocercosis
- Cutaneous tuberculosis
- Besnoitiosis ^[15]

Table No. 1 – Mode of Action and Role of Phytochemicals in the LSDV Treatment.

Sr no	Plants	Chemical constituent	Mode of action	Activity	Refeance
	<p>Salvia officinalis (common saga)</p> 	<p>1,8 Cineole (14.14%), Alpha(18.83%) and Beta(14.14%) Thujone , Camphor(25.14 %).</p>	<p>Neuropathic pains in dorsal root ganglion.</p>	<p>Antioxidant,Antibacterial, Anti-inflammatory</p>	<p>Ghorbani A, Esmailzadeh M. Pharmacological properties of <i>Salvia officinalis</i> and its components. J Tradit Complement Med. 2017 Jan 13;7(4):433-440. doi: 10.1016/j.jtcme.2016.12.014. PMID:</p>
	<p>Piper nigrum (Black pepper)</p> 	<p>Piperine(5-9%), Volatile oil, Pungent resin piper</p>	<p><i>Nicotinic acetylcholine receptor-channel</i></p>	<p>Antioxidant, Anti-inflammatory, Antimutagenic, Antitumor, Antiapoptotic, Antigenotoxic, Antiarthritic, Antifungal, Antidepressant, Anti-HVB (hepatitis B) and Gastro-protective activities</p>	<p>Ghosh K, Bhattacharya TK. Chemical constituents of Piper betle Linn. (Piperaceae) roots. Molecules. 2005 Aug 31;10(7):798-802. doi: 10.3390/10070798. PMID: 18007349; PMCID: PMC6147577.</p>

	<p>Embelia ribes(false black pepper)</p> 	<p>Embelin(2.5-3.1%) and Quercitol 1.0%</p>	<p><i>Proliferator –activator gamma receptor coactivator - 1 a (PGC-1a)</i></p>	<p>Anti-bacterial, Anti helmintic, Analgesic , Anti-inflammatory</p>	<p>Source: Agro-techniques of selected medicinal plants</p>
	<p>Piper betle(pan , sireh)</p> 	<p>Safrole (48.7%), Chavibetol acetate (12.5%)</p>	<p><i>GABAA receptors</i></p>	<p>Antioxidant, Stimulant, and Antiseptic</p>	<p>Ghosh K, Bhattacharya TK. Chemical constituents of Piper betle Linn. (Piperaceae) roots. Molecules. 2005 Aug 31;10(7):798-802. doi: 10.3390/10070798. PMID: 18007349; PMCID: PMC6147577.</p>
	<p>Tinospora cordifolia (guduchi)</p> 	<p>Tinsporine, Tinosporic acid, Gilonin, Giloin</p>	<p><i>DAD2 receptor</i></p>	<p>Antioxidant, Skin disease</p>	<p>Sharma P, Dwivedee BP, Bisht D, Dash AK, Kumar D. The chemical constituents and diverse pharmacological importance of Tinospora cordifolia. Heliyon. 2019 Sep 12;5(9):e02437. doi: 10.1016/j.heliyon.2019.e02437. PMID: 31701036; PMCID: PMC6827274.</p>
	<p>Swertia chirayita(east Indian balmomy)</p> 	<p>Chiatin and Amarogentin</p>	<p><i>The skeletal muscle acetylcholine receptor (AChR)</i></p>	<p>Antioxidant, Anti- tumor, Anti-Allergic, Anti-inflammatory, Anti-bacterial, Anti-Fungal, and Anti-viral activities</p>	<p>Kumar V, Van Staden J. A Review of Swertia chirayita (Gentianaceae) as a Traditional Medicinal Plant. Front Pharmacol. 2016 Jan 12;6:308. doi: 10.3389/fphar.2015.00308 . PMID: 26793105; PMCID: PMC4709473.</p>
	<p>Allium sativum (garlic)</p> 	<p>Allyl propyl disulphide, Disloyal disulphide, Alliin and Allicin</p>	<p>Inhibits acetyl-CoA synthetase</p>	<p>Antibacterial, Antifungal</p>	<p>Shang A, Cao SY, Xu XY, Gan RY, Tang GY, Corke H, Mavumengwana V, Li HB. Bioactive Compounds and Biological Functions of Garlic (<i>Allium sativum</i> L.). Foods. 2019 Jul 5;8(7):246. doi: 10.3390/foods8070246. PMID: 31284512; PMCID: PMC6678835.</p>
	<p>Azadirachta indica(neem)</p> 	<p>Oleic acid (50-60%), Palmitic acid (13-15%), Stearic acid (14-19%), Linoleic acid (8- 16%) and Arachidic acid (1-3%).</p>	<p><i>Its nuclear receptors</i></p>	<p>Antirepellant, Anti pyretic, Antiarthritic, Antibacterial, Antifungal</p>	<p>Alzohairy MA. Therapeutics Role of Azadirachta indica (Neem) and Their Active Constituents in Diseases Prevention and Treatment. Evid Based Complement Alternat Med. 2016;2016:7382506. doi:</p>

					10.1155/2016/7382506. Epub 2016 Mar 1. PMID: 27034694; PMCID: PMC4791507.
	<p>Curcuma longa(turmeric)</p> 	Ar-turmerone (20.50 %), β -Sesquiphellandrene (5.20 %) and Curcumenol (5.11 %).	<i>Tumour necrosis serum</i>	Stimulant , Antiseptic , Anti inflammant, Antihelmentic	Abdel-Lateef E, Mahmoud F, Hammam O, El-Ahwany E, El-Wakil E, Kandil S, Abu Taleb H, El-Sayed M, Hassenein H. Bioactive chemical constituents of Curcuma longa L. rhizomes extract inhibit the growth of human hepatoma cell line (HepG2). Acta Pharm. 2016 Sep 1;66(3):387-98. doi: 10.1515/acph-2016-0028. PMID: 27383887.
	<p>Cordia myxa l (asteroid)</p> 	Alpha-amyrin	Tumor necrosis factor (TNF)- α	Anti-inflammatory, Analgesic	Jamkhande PG, Barde SR, Patwekar SL, Tidke PS. Plant profile, phytochemistry and pharmacology of Cordia dichotoma (Indian cherry): a review. Asian Pac J Trop Biomed. 2013 Dec;3(12):1009-16. doi: 10.1016/S2221-1691(13)60194-X. PMID: 24093795; PMCID: PMC3805104.
	<p>Anogeissus leiocarpa (African birch)</p> 	Gallic acid, Ellagic acid, Chebulic acid, Rutin and Quercetin	Inhibition of the enzyme cyclo-oxygenase	Antioxidant, Anti-inflammatory, and Antineoplastic	Orlando G, Ferrante C, Zengin G, Sinan KI, Bene K, Diuzheva A, Jekó J, Cziáky Z, Simone SD, Recinella L, Chiavaroli A, Leone S, Brunetti L, Picot-Allain CMN, Mahomoodally MF, Menghini L. Qualitative Chemical Characterization and Multidirectional Biological Investigation of Leaves and Bark Extracts of Anogeissus leiocarpus (DC.) Guill. & Perr. (Combretaceae). Antioxidants (Basel). 2019 Sep 1;8(9):343. doi: 10.3390/antiox8090343. PMID: 31480498; PMCID: PMC6770311.
	<p>Cissus populnea(okoho)</p> 	Haxdecanoic acid, Methyl Stearate and Octandecano-ic acid	<i>Peroxisome proliferator-activated receptors</i>	Antioxidant , Anti-inflammatory	Ibrahim H, Mdau BB, Ahmed A, Ilyas M. Anthraquinones of Cissus populnea Guill & Perr (Amplidaceae). Afr J Tradit Complement Altern Med. 2011;8(2):140-3. doi:

					10.4314/ajtcam.v8i2.6320 0. Epub 2010 Dec 30. PMID: 22238494; PMCID: PMC3252698.
	Senna obtusifolia (sicklepod) 	Toxalbumin, and Anthraquinones	Inhibit protein synthesis and ultimately cause cell death	Anti-helminthic, To treat skin infection, Anti cancers Anti pyretic	Ali MY, Park S, Chang M. Phytochemistry, Ethnopharmacological Uses, Biological Activities, and Therapeutic Applications of Cassia obtusifolia L.: A Comprehensive Review. Molecules. 2021 Oct 15;26(20):6252. doi: 10.3390/molecules26206252. PMID: 34684833; PMCID: PMC8538231.
	Tamarindus India (leguminosae) 	Tartaric acid, Acetic acid, Succinic acid, Gum, Pectin, Sugar, Tannins, Alkaloid, Flavonoids, Sesquiterpenes, and Glycosides.	Inhibit muscarinic receptor of M1 and M2 and also attack on nictonic receptor	Anti-inflammatory, Anti-oxidant	Sharma P, Dwivedee BP, Bisht D, Dash AK, Kumar D. The chemical constituents and diverse pharmacological importance of Tinospora cordifolia. Heliyon. 2019 Sep 12;5(9):e02437. doi: 10.1016/j.heliyon.2019.e02437. PMID: 31701036; PMCID: PMC6827274.

Treatment :-

For the lumpy skin disease there are few treatment are used. There antiviral like methylene blue is used to treat it. Methylene blue has show effective against lumpy skin disease virus . Methylene blue act on RBC to form oxidized hemoglobin. The ferric ion back to its oxygen carrying ferrous state. It treat on mass skin disease by reducing the viral load in infected cattle through its mechanism.^[16] The antibiotic are also use to treat the lumpy disease like ribavex, enrofloxacin, amoxicillin, etc. So rabavex is effective in treatment on bacterial. The anticholinergics drugs(beta2-adrenergic agonists) like combivet, urbuerin and multivet are use treat in lumpy skin disease.^[17] Thoses drug can use to reduce the effect of lumpy virus disease. The ayurvedic or allopathic treatment are not available/research on lumpy skin disease virus . However, to avoid the secondary disease like bacterial infection or inflammation, etc. herbal drug like black pepper, garlic, etc can be use. There are some preparations in Ayurveda

❖ Ingredients :- Betel leaves ; black pepper and salt

Preparation:- 1. Blend the ingredient to form a paste
2. Feed the dose in small portion orally^[18]

Even if the vaccine are more effective, but the correct diagnosis and treatment in Ayurveda can cure the disease. It can represent the future treatment for lumpy skin disease and alternative option for secondary drug line. There are many aspects like diagnosis, evaluation and treatment of it.^[19]

Prevention:-

It can prevent the disease by spread it

- To make the separate shed for infected and non infected animal
- To applied anti repellent on non infected animal

- To prevent the transportation from one place to other place
- To vaccinated the infected and non infected animal
- To maintain hygiene near the shed
- To use proper treatment and medication to infected animal^[20]

Therefore, in order to come across these alarming situations, the following recommendations are forwarded;^[29]

- Clinico-hematological and biochemical profile of cattle affected by LSD need to be identified in addition to typical clinical signs.
- Accurate on time diagnosis is needed for control measurements.
- Annual vaccination strategy with homologous strain of the LSDV is obligatory in endemic areas.
- Vector control and animal movement restriction during active period of insect movement is important.
- Bulls used for breeding need to be diagnosed for LSDV.

Conclusion:-

This review concludes that phytochemical treatments are the best remedy without side effect. Lumpy skin disease has led to serious economic losses in affected developed as well as developing countries. The disease causes a considerable reduction in milk yield (from 10% to 85%) due to high fever and secondary mastitis. Other consequences of the disease include damaged hides, decline of the growth rate in beef cattle, temporary or permanent infertility, abortion, treatment and vaccination costs and death of infected animals. The treatment of LSD is only symptomatic and targeted at preventing secondary bacterial complications using antimicrobial therapy^[28]. Treatment trials performed by *goshala*, with the aim of preventing LSD complications and saving life has been successful using combination of antimicrobials, anti-inflammatory, supportive therapy and anti-septic solutions prepared by using phytochemicals. In that turmeric, garlic, black pepper are best ayurvedic treatment used for curing LSDV treatment.

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