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Novel and Emerging Therapies Safeguarding Health of Humans and Their Companion Animals: A Review

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Abstract: Modern medicine has helped to a great extent to eradicate and cure several diseases of mankind and animals. But the existence of incurable diseases like cancer, Acquired Immunodeficiency Syndrome (AIDS), diabetes or rheumatoid arthritis, side effects of allopathic medicine, increasing trend of antibiotic resistance and chemicals and biopesticides causing dietary risk have made the situation more critical than ever before. Thus, it has become a matter of concern for the scientists and researchers to develop novel therapies. Bacteriophage therapy to treat pathogenic bacterial infections, virophage therapy for conservation of global system and avian egg yolk antibody therapy for designing prophylactic strategies against Gastrointestinal (GI) diseases are interesting approaches. Others include the use of cytokines as adjunctive immunomodulators, gene therapy focusing on diseases caused by single gene defects, RNAi technology to suppress specific gene of interest and apoptins for cancer treatment. Stem cell therapy against several diseases and ailments has also been discussed. The use of nanoparticles for better drug delivery, even though costly, has been given equal importance. Nevertheless, immunomodulation, be it through physiological, chemical or microbial products, or through essential micronutrients, probiotics, herbs or cow therapy prove to be cost-effective, causing minimum adverse reactions when compared to allopathy. Development in the field of molecular biology has created an enormous impact on vaccine development. The present review deals with all these novel and emerging therapies essential to safeguard the health of humans and companion animals.

Key words: Apoptin, immunomodulation, panchagavya, phages, sirna, stem cell, yolk antibody, cytokine therapy, gene therapy, stem cell

INTRODUCTION

The state of underdevelopment can be studied in the limelight of its relation with infectious diseases that has a negative impact on the production of industrial goods and animal proteins, especially in underdeveloped countries (Astudillo and Rosenberg, 1983). In this context, infectious diseases act as factors contributing to the state of underdevelopment especially in country like India. The impact of animal and poultry diseases like foot and mouth disease (Verma *et al*., 2008a, 2012), brucellosis (Kumar *et al*., 2009), mycoplasmosis (Kumar *et al*., 2011, 2012a), chicken infectious anaemia (Dhama *et al*., 2002; Bhatt *et al*., 2011) is also very important, mostly because of animal health restrictions based on these endemic diseases. Loss of health in pet animals due to diseases like canine parvovirus (Singh *et al*., 2013), campylobacteriosis (Kumar *et al*., 2012b, c), salmonellosis (Verma *et al*., 2007), canine distemper or Feline Infectious Peritonitis (FIP) hearts the sentiment of owners. Moreover, the lethal diarrhoea caused by colibacillosis (Malik *et al*., 2012), rota viruses, corona virus, the H5N1 avian influenza and the zoonotic disease like campylobacteriosis, salmonellosis

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(Verma *et al*., 2008b) rabies are quiet noteworthy in the context of safeguarding public health (Dhama *et al*., 2005a; Brownlie *et al*., 2006; Lambey *et al*., 2009; Dhama *et al*., 2009; Pawaiya *et al*., 2009; Singh *et al*., 2009; Verma *et al*., 2011a, b; Patyal *et al*., 2011; Hansa *et al*., 2012; Deb *et al*., 2012).

Modern medicine has done much to eradicate and cure disease, but it has failed in some areas due to the existence of incurable diseases like cancer, AIDS, diabetes and rheumatoid arthritis. Cancer affects one in every three persons born in developed countries and is a major cause of sickness and death throughout the world and therapeutic approach is critical due to critical immune response (Cavallo *et al*., 2011; Mahima *et al*., 2012a). HIV infection and AIDS are disproportionately afflicting Third World countries, where substantial adult communities and villages are literally being annihilated as because there is no known cure for HIV/AIDS and due to involvement of high costs of current antiviral therapy (Livingston, 1993). Similarly, therapeutic approaches against diabetes and rheumatoid arthritis are critical (www.cimzia.com).

Long term life regimen of allopathic medicine has potential side effects. Uncontrolled and inappropriate use of antibiotics that have promised much in elimination of major diseases of humans and animals, result in resistance, critical for the future of antimicrobials (Raghunath, 2008; Kumar *et al*., 2012b; Taddele *et al*., 2012). Systemic pesticides used in genetically modified crops like Bt corn, account for 60% (approx.) of dietary risk in domestic crops, ultimately proving troublesome to human health (Monosson, 2005).

Due to advancement in the field of science, field of molecular biology and biotechnology along with nanotechnology are enriched which have led to the generation of many novel therapies (Bartol *et al*., 1999; Chakravarthi and Balaji, 2010; Shirley *et al*., 2011). Therefore, the present review discusses these novel technologies involving bacteriophage, virophage, avian egg antibody, cytokine, gene, siRNA, apoptins, stem cells, nanomedicine, immune system, vaccines, probiotics and herbs safeguarding human and animal health.

Bacteriophage therapy: Bacteriophages can be used for checking bacterial contamination food materials, controlling water-borne infections and food-borne pathogens and remarkably for a variety of severe infections. These are magical viruses that kill bacteria by lysing them and are particularly very useful for treating antibiotic-resistant infections in animals and humans (Tiwari *et al*., 2012). Oral administration or topical application of phages have been attempted for a wide range of bacterial infections, caused by wounds or surgical intervention (Mathur *et al*., 2003; Tiwari *et al*., 2011, 2012) including inflammation of larynx, gums, teeth, sinuses, conjunctiva, infections of skin, gastrointestinal tract, urinary tract, skin infections, burns, boils; and interestingly, cocktailed against some bacteria viz., *P. aeruginosa*, *Staph. aureus* and *E. coli* (Sulakvelidze *et al*., 2001; Hanlon, 2007; Rhoads *et al*., 2009; Lu and Koeris, 2011; Sulakvelidz, 2011). Bacteriophages can be particularly very effective in treating drug-resistant bacterial infections in humans and animals including poultry. Therapeutic applications include treating various bacterial infections, viz., *E. coli*, *P. aeruginosa, K. pneumoniae, S. aureus, S. pyogenes, Bacillus anthracis, Salmonella* spp., *Campylobaeter jejuni, C. coli, Listeria monocytogenes* and others (Tiwari *et al*., 2012).

Virophages: Virophages/satellite viruses depend on the coinfection of their host by another virus inhibiting or damaging the reproduction of the auxiliary virus, examples include Sputnik, Mavirus and Organic Lake phages (Krupovic and Cvirkaite-Krupovic, 2011; Fischer, 2011; Fischer, 2012; Desnues *et al*., 2012). Sputnik can have major effects on ocean nutrient cycles and climate and may play a crucial role in conservation of global systems by regulating the host virus interaction, carbon influx in organic lake, growth and death of planktons (La Scola *et al*., 2008; Monier *et al*., 2008).

Yolk antibody therapy/avian egg antibody therapy: Now-a-days, there is progress to use chicken egg as source of antibodies for the prevention and treatment of gut associated infections (Michael *et al*., 2010), wherein, after immunization, the specific antibodies, otherwise known as IgY are transported to the egg yolk and they can then be separated without sacrificing the bird. Oral administration of IgY has been tried and found useful in treatment of man and animals against microbes including viruses like rotaviruses, bovine coronavirus; bacteria like enterotoxigenic *Escherichia coli*, *Campylobacter jejuni, Yersinia ruckeri*, *Salmonella* spp., *Pseudomonas, Edwardsiella tarda* and *Staphylococcus aureus* (Mine and Kovacs-Nolan, 2002; Kovacs-Nolan and Mine, 2004). The Egg Yolk Antibody (EYA) therapy has also shown promising therapeutic results in cases of infectious pathogens/diseases of poultry viz., infectious bursal disease (IBD), New Castle disease (ND), avian influenza subtype H9N2, salmonellosis, campylobacteriosis, and *Pseudomonas aeruginosa*, *Salmonella enteritidis, Staphylococcus aureus* and *Eimeria tenella* or *E. maxima* (Yegani and Korver, 2007; Rahimi *et al*., 2007; Da Silva and Tambourgi, 2010; Dhama *et al*., 2011a).

Cytokine therapy: The cytokines are used as adjunctive immunomodulators in a variety of infectious diseases (Hafler, 2007; Dhama *et al*., 2008a). The classical examples include the use of recombinant α-interferons and nucleoside analogs for hepatitis B virus (HBV), pegylated interferons and ribavirin for hepatitis C virus (HCV) (Forton and Karayiannis, 2006; Trapero-Marugan *et al*., 2006), HIV-associated cryptococcal meningitis (Antachopoulos and Roilides, 2005) and Crohn's disease (Pizarro and Cominelli, 2007). The immunoglobulin Fc fragment based cytokines provides superior therapeutic approach (Jazayeri and Carroll, 2008). Nevertheless, the development of new vaccines necessitates the development of new types of adjuvants to ensure an appropriate immune response (Nicholls *et al*., 2010), examples include the use of cytokines like IL-7, 12 and 15 as mucosal vaccine adjuvants, Granulocyte-macrophage Colony-stimulating Factor (GM-CSF) along with Monocyte Chemotactic Proteins (MCPs) and Macrophage Inflammatory Proteins (MIPs) to increase recruitment of blood-borne dendritic cells and monocytes to interstitial sites of vaccine delivery etc.

Gene therapy: Gene therapy finds its application in various diseases caused by single gene defect (Thalassemia, sickle cell anemia, cystic fibrosis, haemophilia and muscular dystrophy). The various therapeutic approaches in this context include somatic gene therapy, germ line therapy and use of both viral and non-viral vectors. Transfection of the cell is achieved by electroporation, gene gun, sonoporation, magnetofection, use of oligonucleotides, naked DNA injection, lipoplexes, dendrimers and inorganic nanoparticles (Agha-Mohammadi and Lotze, 2000; Goverdhana *et al*., 2005). Gene therapy is used in case of lymphoma, retinitis pigmentosa, diabetes etc., (Woods *et al*., 2006; Cepko, 2012; Callejas *et al*., 2013).

siRNA therapy: Suppression of specific genes of interest by synthetic dsRNA has made RNAi a valuable research tool. Short interfering RNA was easier to introduce in comparison to long dsRNA strands into mammalian cells (Paddison *et al*., 2002). This RNAi has been successfully used in treatment of various viral infection like respiratory syncytial virus, herpes simplex virus type 2 and measles infection. Apart from infectious diseases they are also helpful in inhibiting virus induced cancerous growth, have receptor-knockdown activity and plays role in gene silencing (Sah, 2006; Jiang and Milner, 2002; Crowe, 2003; Kusov *et al*., 2006; Jia *et al*., 2006; Li *et al*., 2006; Hu *et al*., 2005; Raoul *et al*., 2006).

Apoptins: Drugs directed against defective apoptotic pathways (apoptins) may act as a double-edged sword and forms an interesting target of cancer treatment (Wong, 2011). Approaches for apoptin based therapy to treat cancer include use of agents like oblimersen sodium Bcl-2 antisense oblimer, oblimersen in myeloid leukaemia, use of mutant p53 in pancreatic cancer, silencing of Bmi-1 in MCF breast cancer cells, use of XIAP antisense oligonucleotides in lung cancer and transfection of anti-sense survivin in squamous cell carcinoma (Rai *et al*., 2008; Morton *et al*., 2010; Suzuki and Matsubara, 2011; Ohnishi *et al*., 2006; Sharma *et al*., 2005). Apart from that, chicken anaemia virus VP3 protein is also used in treatment of cancer (Natesan *et al*., 2006).

Stem cell therapy: Introduction of new adult stem cells into damaged or injured tissue forms the basis of stem cell therapy (Lindvall and Kokaia, 2006). Haematopoietic stem cell therapy is used for treating cancer; other uses in human and veterinary medicine include treatment of neurological damages viz. Parkinson's and Alzheimer's disease, spinal cord injury, treatment of equine tendinopathies, Crohn's disease, heart damage, diabetes, inhibiting acute pancreatitis, lung therapy, Acute Respiratory Distress Syndrome (ARDS), corneal epithelial reconstruction etc (Androutsellis-Theotokis *et al*., 2008; Cummings *et al*., 2005; Centeno *et al*., 2008; Ribitsch *et al*., 2010; Jiang *et al*., 2012; Fryer *et al*., 2013; Wen *et al*., 2013; Ardhanareeswaran and Mirotsou, 2013; Cardenes *et al*., 2013; Menzel-Severing *et al*., 2013). However, there are many barriers like biological, technical and clinical that have to be crossed before using this therapy in clinics (Ouyang and Yang, 2013).

Nanomedicines: Since 2000, there is boom of nanotechnology in science, engineering, technology and even in society. This technology can be used in medical and veterinary field for diagnosis, treatment, and prevention of various diseases (Kato, 2013) especially through drug delivery, imaging and vaccine adjuvant (Irache *et al*., 2011; Underwood and van Eps, 2012). Nanomedicine forms the application part of nanotechnology. The common nanomedicine vehicles are solid drug nanoparticles, polymer-based carriers and nanoemulsions that can be used for treatment of various infectious diseases including retroviruses (Siccardi *et al*., 2013). Gold-conjugated nanoparticles improve the therapeutic properties of drugs by selectively targeting certain organs based on their size and charge (Minchin, 2008; Allen and Cullis, 2004), especially anticancer agents. For example, use of carbon nanoparticles (Hollmer, 2012) for paclitaxel or liposome for

doxorubicin (Garde, 2012); polymers and liposomes for delivery of camptothecins and platinum (II) drugs (Kieler-Ferguson *et al*., 2013) and so also use of polyethylene glycol for better delivery of several antibiotics (Trafton, 2012).

Immunotherapy: The main objective of immunotherapy is to control an immune response (Fraile *et al*., 2012). Use of monoclonal antibodies is an interesting approach (Deb *et al*., 2013), wherein, they are coupled with drugs (magic bullets) (Nielsen *et al*., 1986). Other immunomodulators include a diverse groups of physiological (neuroendocrine hormones and glucocorticoids, neurotransmitters and neuropeptides, thymic products (Dan and Lall, 1998; Singh *et al*., 1998; Wilckens and De Rijk, 1997), microbial (heat killed or formaldehyde treated anaerobic suspension of *Propionibacterium acnes*) (Becker *et al*., 1989) and plant/herbal products (Mahima *et al*., 2012a). Synthetic chemical compounds like levamisole, imuthiol, avridine, biostim etc. are good immunomodulators (Coppel and Kulkarni, 2012).

Therapeutic vaccines: Prevention of diseases by vaccination has been an integral part of health management programs as this has successfully prevented many important diseases in a cost-effective manner (e.g., inactivated vaccine against warts in cattle) (Ferro and Mordini, 2004; Singh *et al*., 2008; Pathania *et al*., 2011). Molecular biology has created an enormous impact on vaccine development, leading to development of DNA vaccines (targeted animal diseases include FMD, tuberculosis, Brucellosis, Rabies, Canine distemper, Johne's disease), subunit vaccine (against Infectious bovine rhinotracheitis and rabies), anti-idiotypic and virosome vaccine, virus-based nanoparticles and virus like particles, biotechnologically engineered vaccine against pseudorabies etc., (Dhama *et al*., 2008b; Mengeling *et al*., 1997). Importantly, plant based oral vaccine have gained popularity in human medicine and has been found to be protective against diseases like Hepatitis B, Human Immunodeficiency Virus (HIV), Cholera, Tetanus, Malaria, Measles, Japanese encephalitis (JE) and Influenza (Mercenier *et al*., 2001; Daniell *et al*., 2009).

Design and development of therapeutic cancer vaccines has proven to be an enormous challenge (Pejawar-Gaddy and Finn, 2008). But with the development of whole tumour cell vaccines, as is tumor-derived Chaperone-rich Cell Lysate (CRCL) vaccine, genetically modified tumor cell vaccines viz. immunizations with canine tumor cell lines transfected with human GM-CSF, peptide vaccines by using Wilms' tumor gene, heat shock protein vaccine, dendritic cell vaccine etc. (De Gruijl *et al*., 2008; Li *et al*., 2008; Hogge *et al*., 1999; Oka and Sugiyama, 2010; Blachere and Srivastava, 1995; Adamson *et al*., 2009) have made the management of wide variety of tumors easier than earlier.

Nutritional immunomodulation/therapy: Nutrition plays a pivotal role in modulation of immunity and there must be adequate supply of nutrients for the proper functioning of immune system. Nutritional deficiency affect immune cells and inhibits vital functions,like the cytokine responses (Katona and Katona-Apte, 2008) for which there is need to supply essential micronutrients viz. Vitamins A, D, E, C, B6, folate, B12 (Ramakrishnan *et al*., 2004; Veldman *et al*., 2000; Meydani *et al*., 2005; Haertel *et al*., 2004; Leklem, 2001; Dhur *et al*., 1991; Tamura *et al*., 1999) and trace elements viz. selenium, zinc, copper and iron (Chaudhary *et al*. 2010, Mahima *et al*., 2012b and Mahima and Mudgal, 2012; Cuevas and Koyanagi, 2005; Bonham *et al*., 2002; Openheimer, 2000) in the diet. Leptin is considered as an emerging cytokine-like immune regulator found to be effective in nutritional problems (Cunningham-Rundles *et al*., 2005).

Probiotics: Probiotics (direct feed microbials) are naturally occurring and selected beneficial live microorganisms that create a positive impact on the physiological status of the host (Dhama and Singh, 2010). Probiotics include bacteria, fungi and yeast that create an unfavourable atmosphere for the pathogenic microbes in gastrointestinal tract (Bengmark, 1998). Generally, live apathogenic bacterial strains belonging to genus *Lactobacillus*, *Streptococcus* or *Enterococcus*, are used in livestock and poultry (Balevi *et al*., 2001; Dhama *et al*., 2008c, 2011b. *Bacillus, Aspergillus, Saccharomyces* and others are also being used.

Various studies have proved this for example increase in circulating antibody secreting cells by *Lactobacillus* in diarrhoea (Kaila *et al*., 1992) and enhancement of intestinal IgA production by *Bifidobacterium bifidum* (Park *et al*., 2002) etc. Probiotics have been found to enhance immunity and prevent various enteric infectious diseases caused by bacterial, fungal, protozoan and viral agents. These have been proven to be protective and combating various harmful pathogens viz. *E. coli*, *S. aureus*, *Salmonella* spp., *Clostridium perfringens*, *Listeria monocytogenes*, *Campylobacter jejuni*, *Yersinia enterocolitica, Candida albicans,* coccidian parasites (*Eimeria* spp.) etc. (Dhama *et al*., 2008c, 2011b). For best results, a multi strain probiotic should be used timely.

Herbal therapy: Globally many researches are going on role of plants and their extracts in enhancing the immunity of man and animals (Mahima *et al*., 2012a). Historically, various plants have been used in traditional system of India in the name of Rasayanas, which increases the resistance of the body against various pathogens (Tan and Vanitha, 2004). Various herbs viz., tulsi, ginger, chilli, turmeric, onion, garlic, spices, coriander etc are traditionally used for the treatment of different ailments based on Indian Traditional knowledge. Plants are source of phytochemicals that can have anti-microbial, antiviral or antifungal and immunomodulating activities. Some of the examples of medicinal plants are *Tinospora cordifolia, Piper sarmentosum, Glycyrrhiza* species, *Gymnema species*, *Centella asiatica*, *Camellia sinensis*, *Crataegus species* and *Olea europaea*, which can be used for treating the chronic diseases viz., diabetes, blood pressure, high cholesterol, rheumatoid arthritis etc (Mahima *et al*., 2012a). Plants are also used for the treatment of many parasitic diseases including malaria, toxoplasmosis, helminth infestations, chagas disease etc. Vinca alkaloids (vinblastine and vincristine) from the Madagascar periwinkle, (*Catharanthus roseus* G.); Paclitaxel from bark and other parts of *Taxus brevifolia*, *Taxus Canadensis* and *Taxus baccata*; Camptothecin, (from *Camptotheca acuminate*); Epipodophyllotoxin (from Podophyllum species) and Homoharringtonine (from the Chinese tree *Cephalotaxus harringtonia* var. Drupacea) have been used as anticancer drugs for treatment of ovarian cancer, breast cancer and lung cancer. Fresh *Allium sativum*, called ajoene, appears to protect CD8+ cells from attack by HIV, gives protection against human cytomegalovirus (HCMV) in a dose dependent manner (Guo *et al*., 1993) for example *Piper longum* has anti-tumour activity (Sunila and Kuttan, 2004). The roots of *Astragalus, Isatis and Achyranthes* significantly improve the immunity (Hashemi and Davoodi, 2012).

Cow therapy: The concept of cow therapy is based on the use of five constituents viz., milk, curd, ghee, urine and dung extract obtained from Indian Zebu cow, thus also known as Panchagavya (Verma, 2005). Panchagavya plays an important role in Ayurveda system of medicine and has got mention in ancient Indian literature as it enhances the body resistance and refractoriness to infections (Dhama *et al*., 2005b). Panchagavya/cowpathy has been reported to be useful for the treatment of several disorders and diseases like allergies, colds, cough, renal disorders, gastrointestinal track disorders, wound healing, skin infections, aging, intoxications, tuberculosis, chicken pox, hepatitis, leprosy etc. It is also being explored to treat deadly diseases like AIDS, diabetes, asthma, heart diseases, arthritis and others. Panchagavya and Ark have been found to be useful against flu viruses (Chauhan *et al*., 2001; Dhama *et al*., 2005b). Cow urine has been demonstrated to have potent anti-cancer activity and bioenhancer of drugs (Dhama *et al*., 2005c). Gauloka Peya (meaning 'drink from the land of cow') is having medicinal properties and is prepared by incorporating distilled and sterile cow urine mixed with water and herbs like brahmi and basil (Rahman, 2010).

CONCLUSION AND FUTURE PERSPECTIVES

The development in the field of molecular biology and nanobiotechnology has increased the versatility of therapeutic approaches to control various diseases and ailments. Thus, contributing to the improvement of health status of individual and accelerated growth of biological science at a rapid pace has the potential for significant advances in medical and veterinary public health. DNA technologies have revolutionalized modern science and find its application in the management of many incurable and chronic diseases of humans as well as animals. Stem cell therapy has the ability to change the face of human diseases as well as to alleviate sufferings. Nowadays, principles that govern the immune response are used in tailor-made vaccines against many noninfectious human diseases viz. cancers and autoimmune disorders. Nutritional immunomodulation helps in better economic outcome in the livestock sector. The concept of probiotic supplementation in feed is promising to maintain growth and production along with protecting health and boosting immunity without any side effects or public health hazard. Similarly, Ayurveda and Rashayanas are also preferred by a large portion of Indian population as they are cost effective and free from side effects. The IgY technology offers great future opportunities for designing prophylactic strategies against infectious GI diseases in humans and animals. Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in near future. The application of all these therapies under various circumstances will ultimately safeguard health. Nevertheless, it should always be kept in mind that application of various novel therapies require judicious approaches to become fruitful in a better way.

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