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Factorial Review Design Analysis of Different Types of Lymphadenopathy and Causative Factor

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Abstract Lymphadenopathy is considered as chronic infection in which individuals are incompetent to follow up about stepwise clinical management procedures such as factorial design of different types of microorganisms and related infections, control measurements of preventive care, detoxification procedures, immune-stimulant merits and demerits and immuno suppressant action merits and demerits. This infection can be managed via stepwise clinical procedures such as SOP for cleaning of washing hands and WHO SAFE handling system procedures, controlling of antimicrobial resistance, Dosing errors such as over use and under use medications, Obesity related factors, Enzymatic inhibition and stimulation activity, systematic ADME modification, Vaccination procedures in different races and culture intake of foods, pharmacodynamics variation, Genetic and Heredictary disorders and drug addiction. This paper describe about different plants are categorized to manage stepwise infection on the basis of toxicological data pertaining to Idio-syncratic response reaction factors such as form and innate chemical activity, exposure route,presence of other chemicals in form of toxins, Psychological changes, role of circadian rhythum with gut toxicity, toxin rich intake nutrition packed and unpacked foods.

Keywords: *lymphadenopathy, immuno-suppressive agents, oxidative burst activity, macrophage migration inhibitory factor, ADR*

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1. Introduction

Lymphadenopathy is a major causative disease of abnormal enlargement of lymph nodes nearly about 600 in human body. Out of 600 lymphnodes, 300 lymph nodes are located insupraclavicular lymphnodes region. Lymphatic system can eradicate the working function when lymph nodes, ducts, vessels, or lymph tissues become concealed the vessels pathway,making disguising the tissues due to inflammation and proliferation [1].

Comparatively males are affected more than female gender. The primer concept is emotional stress due to heavy stressful workload, extended time working condition, poverty-based lifestyle, nutrient intake based on malnutrition factor-vicious cycle, attitude to maintain high lifestyle, inability to carryout physical body building, improper self-medication usage, over-under use of prescription medication, improper diet chart follow up [2,3].

According to 19th century Hippocratic traditional medicine system in relationship with scientific fact psychoneuroimmunology, Human emotion-6th sensible emotional connection have a profound effect on WBC immune cells such as CD3-, CD19+, CD 14-marker of B cells, CD3 marker of T-cells, CD3+, CD4 helper T cell, CD3+CD45RA+CCR7+ marker of Naïve T cell, CD3+CD45RA-CCR7+ marker of central memory T cell, CD3+CD45RA-CCR7-marker for Effector memory T cell, CD3+CD45RA+CCR7-marker for Effector T cell. General factors related sorrow feelings of stress, social isolation, and stress hormone such as adrenaline and cortisol will tend to reduce immune function that decrease immune stimulation.

Lulling-a kind of relax feelings and Relax and mellow heart feeling tuckaway with success to bring forth neuronal signalling molecules such as serotonin, Dopamine and relaxing that to cause a strengthening effect on immune system.

1.1. Lymphatic System [4]

The complement system composed of an elaborative network of vessels that connected through almost all our tissues to allow for the movement of a fluid called lymph and participated for innate, disposal and adaptive immunity. Lymphoid organs are categorised into two types such as central lymphoid organ which are classified into thymus and bone marrow and peripheral lymphoid organs which are categorised into lymphnodes, spleen and mucosa associated lymphoid tissue instance Tonsils and Peyers patches of small intestine.

Central lymphoid organs-thymus gland involves to exhibit humoral immunity, delayed hypersensitivity type

reactions and cell mediated immunity Graft rejections. Central lymphoid organs-bone marrow involves to exhibit hematopoiesis. Primary CLO can exhibit central tolerance and produces differentiation and maturation from stem cell.

Peripheral lymphoid organs such as lymph nodes, spleen and MALT (mucosal associated lymphoid tissue), GALT (Gut associated lymphoid tissue), BALT (Bronchous associated lymphoid tissue), SALT (Skin associated lymphoid tissue) and NALT (Nasal associated lymphoid tissue), adenoids and tonssils are involved in adapt immunity against viral infection. Secondary PLO can exhibit peripheral tolerance and involve in proliferation action activation by antigen.

2. Category of Lymphadenopathy

Lymphadenopathy is categorised into cervical, mediastinal, bilateral hilar and retroperitoneal lymphadenopathy.

2.1. Cervical Lymphadenopathy: [5]

Cervical lymphnodes swelling usually signals a collagen vascular infection due to bacterial or viral infection and happening quickly and unexpectedly malignancy. Children with Hodgkin disease present with cervical adenopathy in 80%-90% of cases as opposed to 40%of those with Non-Hodgkin lymphoma.

2.2. Hilar Lymphadenopathy: [6]

Based upon distinguishing radiographical findings reviewed from article-

Bilateral hilar lymphadenopathy is an abnormal bilateral enlargement of hilar lymphnodes pulmonary hila lymphnodes that is confirmed due to fungal,mycobacterial and sarcoidosis.This is caused by viral infection, mycobacterial, toxoplasmosis and cat scratch diseases.

2.3. Mediastinal Lymphadenopathy: [7]

Retrospective study revealed truth fact about concept of mediastinal that enlargement at mediastinum is associated with pathological parameters such as dental caries carbohydrates -streptococcus mutants relate to decrement of salivary flow. Histoplasmosis is a variety of self-limiting diseases.

Benign outgrowth may have correlated to progression of fibrosis that is larger than 10mm-15mm.

2.4. Retroperitoneal Lymphadenopathy: [8]

Gallium scan data explained concept of Retroperitoneal lymphadenopathy in relation with hepatosplenomegaly as well as IG4 related diseases. This is a condition that enlargement of lacrimal and salivary glands, orbital diseases, autoimmune pancreatitis (AIP), ormonds disease and tubulo intestitial nephritis. This kind of infection tend to cause Non tubercular mycobacteria-AIDS in association with mycobacterium abscessus and hypercalcemia due to imbalance activity of parathyroid hormones.

2.5. Supraclavicular Lymphadenopathy: [9]

The skew report analysis described about virchow's node is one of the asymptomatic condition such as cytomegalovirus and mltiplesclerosis caused by metastasis process.

Cervicothoracobrachial region [10] is a neurogenic type condition in which there is compression of nerves, arteries or veins in the passageway from lower neck to armpit can be lead to arm swelling pain cyanosis. This is classified as

a) Neurogenic thoracic outlet syndrome.
b) Paget -schroetter syndrome
c) Aneurysm formation

When nerves are compressed, signs and symptoms of neurogenic thoracic outlet include, carpel tunnel syndrome, Thromboangirtis obliterans, Raynauds diseases, pinched nerve and forest bite. Signs and symptoms of venous thoracic outlet syndrome (Paget-schroetter syndrome) can include: [11]

- Discoloration of hand (bluish colour)
- Arm pain and swelling
- Blood clot in veins in the upper area of body
- Arm fatigue with activity
- Paleness or abnormal color in one or more fingers or hand
- Throbbing lump near your collarbone

Table 1. denote about different types of lymphadenopathy and causative microorganisms

s.no	Types of lymphadenopathy	Causative microorganisms	Morphological shape of microorganisms
1	Cervical lymphadenopathy	Golden yellow colony bacterium [12] Gram (+)aerotolerant non sporing bacteria GBS-Beta haemolytic bacteria	Staphylococcus aureus Gram (+)round shape Streptococcus pyogenes Gram-positive, aerotolerant bacteria Group B Streptococci Spherical shape
2	Hilar Lymphadenopathy	Mycobacterium *Propionibacteria* *Borrelia bacterium* *Lenti virus* *Mycobacterium pnuemoniae(saprotropic)* *Tropheryma whipplei* *[13,14,15]*	Mycobacterium Shorter oval Propionibacteria gram-positive, anaerobic, rod-shaped Borrelia bacterium Spiral shape Lenti virus Capsid shape Mycobacterium pneumoniae Round, pear shaped and even filamentous Tropheryma whipplei Rod shape

s.no	Types of lymphadenopathy	Causative microorganisms	Morphological shape of microorganisms
3	Mediastinal Lymphadenopathy	Mycobacterium malmoense [16,17]	Mycobacterium malmoense Gram positive bacterium
4	**Retroperitoneal Lymphadenopathy**	Histoplasma capsulatum [18] Mycobacterium tuberculosis [19] *Staphylococcus aureus* [20] *BACTERIMIA* GRAM POSITIVE *Group A streptococcus* (GAS)pyogenes *Group BStreptococcus agalactiae (neonates)* [21] *Viridans streptococci* [22] *streptococcus bovis* [23] phylum Firmicutes [24] Vancomycin resistant enterococcus [25,26] GRAM NEGATIVE *E.coli* [27,28] *Pseudomonas aeruginosa* [29] *Klebsiella pneumoniae*, [30] and *Proteus mirabilis.* [31] *Salmonella* [32]	Histoplasma capsulatum mycelial shape Mycobacterium tuberculosis Non-motile Rod shape Staphylococcus aureus Round shape Streptococcus pyogenes Round shape Streptococcus agalacitae spherical or ovoid Viridans streptococci Gram positive spherical bacteria Streptococcus bovis Spherical or ovoid Phylum firmicutes Cocci or rod shape Vancomycin resistant enterococci Gram positive coccoid shape E.coli Rod shaped Pseudomonas aeruginosa Rod shaped Klebsiella pneumoniae Rod shape Proteus mirabilis Anaerobic rod shape Salmonella Rod shape
5	Supraclavicular Lymphadenopathy	Brucella [33] Lentivirus [34] Mycobacterium Treponema pallidum [35] human betaherpesvirus 5 (Cytomegalovirus) [36] hepatotropic virus A,B,C,D AND E. [37] Epstein-Barr virus, and yellow fever. [38] Histoplasma capsulatum spores. [39] *Actinomyces israelii* [40,41] *A. gerencseriae [42]* Toxoplasma gondii, (Berdoy et.al., 2000) Giardia duodenalis [43,44,45,46,47] Chlamydia trachomatis.[48]	Brucella Non capsulated non motile coccoibacilli Lenti virus Capsid shape Mycobacterium Shorter oval Treponema pallidium spiral Human beta herpes virus 5 (Cytomegalovirus) spherical in shape with icosahedral symmetry. Hepatotropic virus A spherical Hepatotropic virus B Double stranded DNA Hepatotropic virus C Single stranded positive RNA Hepatotropic virus D Helical and icosahedral Hepatotropic virus E Polyhedral virus Epstein-Barr virus Icosahedral capsid Yellow fever virus Single stranded RNA virus Histoplasma capsulatum spores Round to oval Actinomyces israelii Rod shape Actinomyces *gerencseriae* Circular in shape Toxoplasma gondii Cresent shape Giardia duodenalis Oval in shape Chlamydia trachomatis Coccoid or rod shape

Signs and symptoms of arterial thoracic outlet syndrome can include:

Musculoskeletal ATOS Syndrome: This condition is classified as Subacromial impingement, Rotator cuff tear and adhesive capsulitis.

- Cold fingers, hands or arms
- Hand and arm pain
- Lack of colour (Pallor) or bluish discolouration (cyanosis) in one or more of fingers or your entire hand

- Weak or no pulse in the affected arm
- Causative microorganism of lymphadenopathy

3. Pathological Symptoms

Epidemiological data suggested about factorial design to identify unexplained lymphadenopathy. Algorithmic analysis data predicted the majority of lymphadenopathy both localised and generalised. Generalised lymphadenopathy is of benign, self-limited etiology. This is classified into 3 categories according to history and physical examination. a) Diagnostic b) suggested and unexplained lymphadenopathy condition.

Persistent generalised lymphadenopathy (PGL)is enlarged, painless, muscles from trabeculae carneae and septomarginal trabeculae lymphnodes occurring in a couple of different areas for more than three to six months for which no other reason can be found.This sickness defects happened in latency period of HIV/AIDS.

3.1. Epidemiological Clues to Diagnostic Approach Lymphadenopathy

Algorithmic analysis of diagnostic approach consider about patients age, physical examination such as Ig-M toxoplasma antibody, Ig-M CMV antibody and viral culture of biological fluids and patients history relate with onset of infection, medications taken type and dose, duration of treatment and occupational expostures (Hunters, trapers, fisherman, fishmongers and slaughtahouseworkers, recent travel related (different race) or high risk behaviours that suggest specific disorders. On the basis, it is classified as,

1) Bartonellosis, Toxoplasmosis

2) Undercooked meat-Toxoplasmosis

3) Lime borreliosis [49]

4) chronic risk condition- sexual behaviour -HIV, syphilis, Herpes simplex virus,cytomegalovirus, hepatitis infection.

5) Blood transfusions,Plasma transfusions, platelet transfusions, cryoprecipitate transfusions, white blood cell transfusion-cytomegalovirus, HIV [50].

6) Intrvenous drug use-HIV, endocarditis and hepatitis B infection

7) occupational expostures -Tularemia and erysipeloid

8) Journey related-Coccidioidomycosis [27], bubonic plague, Histoplasmosis, scrub typhus, African trypanosomiasis, American trypanosomiasis, Kala azar-leishmaniasis and typhoid fever.

3.2. Algorithmic Data Regarding Suggested/Suspected Lymphadenopathy

These types are evaluated on the basis patients having symptoms such as fatigue, fever, malaise and atypical lymphocytosis (Mononucleosis type),splenomegalopathy (Epstein-barr virus), Asymptomatic (Toxoplasmosis), Hepatitis(CMV), Flu like illness and rash-Initial stages of HIV infection, cervical and axillary nodes (cat-scratch diseases) and Fever, pharyngeal exudates and cervical nodes (Pharyngitis due to group A streptococcus and gonococcus) [51].

3.3. Epidemiological Data Pertaining to Unexplained Lymphadenopathy

After clinical test completed about diagnostic and suggested lymphadenopathy, rest of symptom carrier host comes under unexplained lymphadenopathy. This unexplained lymphadenopathy is scrutinised on the basis of size of nodes and consistency lymph nodes, prehistory, duration of infection and duration of medications taken.

The interpretation results of sizes and indications can vary from 0.5 cm -epitrochlear nodes -abnormal >1 cm^2 - No cancer, 1.5 cm- abnormal Inguinal nodes >1 cm^2 -2.25 cm^2 cancer, > 2.25 cm^{2-} infection and inflammatory conditions and > 2 cm^2 in diameter - aberrant chest radiograph and in default of ear, nose and throat symptoms, TB, Cat scratch diseases or sarcoidosis.

The interpretation results of consistency and indications can vary from stony hard nodes-metastatic cancer,rubbery nodes very firm -lymphoma, softer nodes-infections and inflammations, suppurant nodes-fluctuant,shotty-smaller nodes that feel like buckshot under skin(cervical nodes of children with viral illnesses).

The following chemical groups can helpful for treatment of unexplained lymphadenopathy:

a) Isomer of hypoxanthin,

b) (4-carbamoyl methyl phenoxy) methyl group at first position and N-isopropyl substituents.

c) Sulfhydryl containing analog of proline

d) Carbamoyl substituents and azepine nitrogen

e) βLactam ring and dihydrothiazine ring and acyl side chain (7-aminocephalosporanic acid)

f) orange yellow transition metal and group 11 element (aurum)

g) 1-hydrazinophthalazine hydrochloride

h) Thiazolidine ring fused to βlactum ring towhich a variable group is attached by a peptide bond.

i) Sodim 5,5 diphenyl 2,4 imidazolidinedione

j) 5-ethyl dihydro 5-phenyl 4,6(CH,5 H)-Pyrimidinedione.

k) Cinchonine with H at 6^{th} position of quinoline ring substituted b methoxy.

l) 2,4 diamino -5 (3,4,5-Tri methoxy benzyl) pyrimidine

m) N1-5 methyl -3 iso oxazolyl sulphanilamide

n) Sulfinylindene

3.4. Generalized Lymphadenopathy: 25%

Autoimmune lymphoproliferative disorder is characterised by generalised lymphadenopathy such as, elevated serum aminotransferases, lymphocytosis, splenomegaly and autoimmune phenomena. Alberto quaglia et.al explained that this is happened by inherited mutation of CD 95 (FAS) gene which in turn cause abnormalities in liver biopsies due to infilteration of CD3+ T cells with periportal fibrosis and extramedullary haemopoiesis.

Parasitic infections [52] that may present with generalized lymphadenopathy include filariasis (tropics, subtropics; vector: mosquito), Leishmania (kala-azar, Oriental sore, chiclero—Latin America, Middle East, India; vector: sandfly), Schistosoma (Asia, Africa, Caribbean, South America; intermediate host: snail), and Trypanosoma (Chagas disease—Latin America; sleeping sickness—Africa; vector: tsetse fly). Consider these when there has been travel to endemic areas or the child lives in

such an area. Eosinophilia may be associated with parasitic infection.

One distinct type of generalised lymphadenopathy - Parasitic infections can spread from a) mosquito can cause filarises in tropics and subtropics b) sandfly can cause leishmania in american race, c) snail from schistosoma in asia,Africa,Caribbean and south america d) tsetse can cause chagas diseases in American race and sleeping sickness in Africa race.

The specialised type of generalised lymphadenopathy is Was-Wiskott-aldrich syndrome a kind of X-linked recessive diseases which characterised by low platelet count.

The peculiar type of generalised lymphadenopathy is CHS - Beguez -chediak -Higashi syndrome a kind of autosomal recessive disorder which happened due to hypopigmentation of skin,hair and eyes in association with mutation with lysosomal trafficking regulator protein inturn producing decrement action of phagocytosis.

The other classification of generalised lymphadenopathy is categorised as follows:

Malignancy GL (e.g. metastases, leukemia, Kaposi's sarcoma and lymphoma)

Autoimmune diseases-(e.g.SLE,RA, dermatomyositis, stills diseases and Sjigren's syndrome.

Infectious-(e.g. Brucellosis, cat scratch diseases, EBV [53], CMV, HIV, Rubella, Tuberculosis, Tularema, viral hepatitis [54], Typhoid fever, syphilis, and pharyngitis)

Others–(e.g. Kawasaki's diseases, castlemen's diseases, lipid storage diseases, necrotizing lymphadenitis, histioctosis X, hyperthyroidism and sarcoidosis, amyloidosis).

4. Causative Factor for Disease Spreadability

4.1. Causative Factor NO.1

In comparative with human, birds have bursa of fabricius-specialised organ having 8000-12000 lymphoid connective tissue follicles which is important site of hematopoiesis as well as involving in proliferation of Gut associated lymphoid tissue GALT and differentiation of 1,00,000-1,50,000 B lymphocytes which in turn produce immunoglobulins IG-M -B cells having higher molecular weight 10,00,000 molecule followed by IG-G on the 20 th century and then IG-A.

Human-bone marrow is important site of hematopoiesis and B cell development but unfortunately mammals donot have an equivalent organ. Inability to produce hematopoiesis condition causing complex contagious disease (IBD)-Gumboro disease. Gumboro disease is a picobirnavirses – a kind of RNA Virus that has a bi-segmented genome and belongs to Avibirna virus family Birnaviridae. Infected chicken having Avibirna virus that causes severe inflammation of pseudostratified interfollicular epithelium presented in following regions such as Bursa at Thigh region, IschoGluteal bursitis, Trochanteric bursitis, bursitis tendonitis synovitis, bursitis tendonitis knee effusion, patellar tendonitis, bursitis pes anserinous pain syndromes, intermetatarsal bursitis, MTP (metatarso phalangeal bursitis) and calcaneal bursa. This is the prime reason to produce considerable morbidity and mortality.

Mechanism involved in viral genome replication happening in cytoplasmic through binding with cell surface receptor IG-M located point bursa region. An additional receptor that can be fasten is Heat shock protein 90 (HSP 90) on the surface of DF-1 cell membrane. Inspite of the fact that the receptor hold together either virus or the VP2 viral particle. The penetration of membrane come to aid by CAPSID PEP 46. The capsid will have a peptide give rise from the C-Terminal of PVP2 that is released by VP4.The peptide lead to result in the membrane to become permeable by forming pores which allow for PEP 46 entry depending on calcium dependent. If the inner calcium gradient is low then it is thought to enter V-ATP ase positive vesicles by endocytosis and uncoated for entry into cytosol.

Furthermore, it has been found VP2-alpha 4 beta 1 abet or investigate an investigation in submicroscopic infectious agent virus in the cell as well through micropinocytosis. This will recognise to accept virus to be moved to the early endosomes that is accomplished in the cell Rab 5.Replication follows the double stranded RNA virus replication model. Double stranded RNA virus transcription is the method of transcription. Young chicken and other fowl serve as natural host. Transmission routes are contamination. [55,56]

4.2. Causative Factor no.2

Birnaviridae is a family of double stranded RNA viruses. Salmond fish, birds and insects serve as natural hosts. These are currently 11 species in this family divided among seven genera.

Diseases associated with this family include infectious pancreatic necrosis in salmond fish which bring about significant losses to the agriculture industry with chronic infection in adult salmond fish and acute viral disease in young salmond fish.

Infectious pancreatic necrosis virus (IPNV) a birnavirus is a crucial pathogen in fish farms. Analysis of viral proteins such as structural proteins,non-structural proteins, regulatory proteins and accessory proteins exhibit that VP2 is the major structures and immunogenic polypeptide of the virus. All neutralising monoclonal antibodies are distinct to VP2 and bind to continuous or discontinuous epitopes.

The adaptable domain of VP2 and 20% aminoacids of conserved C-Terminal are probably. The most essential in inducing immune response for protection of animals. Non-structural protein VP5 is found in RNA segment A. The function of this small viral protein is unknown. It is accomplished to be involved in influencing apoptosis.

Viral genome replication is cytoplasmic. Entry into host cell is achieved by cell receptor endocytosis. Replication succeeding the double stranded RNA virus replication model in the cytoplasm. Double stranded RNA virus transcription is the method of transcription in cytoplasm. The virus is released by budding.

Salmond fish (aquabirnavirus), young sexually immature chickens (Avibirnavirus), insects (entomobirnavirus) and blotched snakehead fish (Biosna virus) as the natural host.Transmission routes are contact. [57,58]

4.3. Causative Factor no.3:

Apoptosis signal regulating kinase 1 (ASK I) also known as mitogen activated protein kinase 5 (MAP 3K5) which is located on chromosome 6 at lupus 6q 22.23 and transcribed protein contains 1374 aminoacids with 11 kinase subdomains. MAP 3K5 is a member of MAP Kinase family that enter into mitogen activated protein kinase pathway. It stimulates C-JUN-N-Terminal kinase (JNK) and P38 Mitogen activated protein kinases in a Raf independent fashion in stress responsive MAP3KS such as oxidative stress, endoplasmic reticulum stress and calcium influx. ASK 1has been found to be involved in cardiovascular and neurodegenerative diseases, diabetes, rheumatoid arthritis, cancer. [59-63]

4.4. Causative Factor no.4

Under Non-stress conditions ASK 1 is oligomerised channel through its C-Terminal coiled-coil domain but remains in an inactive form by suppressive effect of reduced thioredoxin (Trx) and calcium and integrin binding protein 1 (C1B1).

Thioredoxin (Trx) inhibits ASK 1 kinase activity by direct binding to its N-Terminal coiled-coil domain (NCC). Trx and C1B1 regulate ASK 1 activation in a redox or calcium sensitive respectively.

Both appear to compete with TNF ALPHA receptor associated factor 2 (TRAF 2) an ASK 1 activator. TRAF 2 and TRAF 6 [64] are then recruited to ASK I to form a larger molecular mass complex. Subsequently ASK I forms homo-oligomeric interactions not only through the CCC but also NCC which leads to activation of ASK 1through autophosphorylation at threonine 845.

Alternatively ASK I gene transcription can be modified by inflammatory cytokines such as TNF alpha and IL-1 through upregulation or downregulation of NF kb protein ReIA.

Interestingly TNF alpha is able to stable the ask 1 protein through deubiqutination process using deubiquitinating peptidases, deubiquitinating isopeptidases, deubiquitinases, ubiquitin proteases, ubiquitin hydrolases, ubiquitin isopeptidases, deubiquitinases, are a large group of proteases that cleave ubiquitin from proteins.

Ubiquitin is attached to proteins in order to regulate the degradation of proteins via proteasome and lysosome, coordinate the cellular localisation of proteins, activate and inactivate proteins and modulate protein protein interactions.

In humans there are 102 putative DUB genes which can be classified into two main classes. Cysteine proteases and metalloproteases consisting of 58 ubiquitin specific proteases (USPs), 4-ubiquitin C-terminal hydrolases (UCHs), 5-Machado-Josephin domain proteases (MJDs), 14 ovarian tumour proteases (OTU) and 14 Jab 1/Mov 34/Mpr 1 pad 1 N terminal (MPN +)(JAMM)domain containing genes.11 of these proteins are predicted to be functional leaving 79 functional enzymes. In yeast, the USPs are known as ubiquitin-specific processing proteases (UBPs)

When ubiquitin specific processing proteases can be expressed high level in extreme condition such as colon cancer and lung cancer. [64,65]

4.5. Causative Factor no.5:

GATA 2 or GATA Binding factor 2 is a transcription factor ie,a nuclear protein which regulates the expression of congenital character. It regulates many genes that are critical for embryonic development, self renewel, maintenance and functionality of blood forming, lymphatic system forming and other tissue forming stem cells.

Inactivating mutations of GATA 2-(MONOMAC syndrome)gene cause a reduction in the cellular levels in the cellular levels of GATA 2 and development of wide range of familial, hematological, immunological, lymphatic and disorders that are grouped together into disease termed GATA 2 deficiency.

MONOMAC syndrome is a rare autosomal dominant syndrome associated with monocytopenia, B and NK cell Lymphopenia, mycobacterial, viral, fungal and bacterial opportunistic infections and virus infection -induced cancers.

GATA 2 deficiency begins benign neoplasm but if untreated progresses to life threatening such as opportunistic infections, virus induced cancers, lung failure, acute myeloid leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia and lymphoid leukemia. Over expression of GATA 2 will promote aggressiveness of non-familial EV 11 positive AmL leading causative factor of prostate cancer. [66,67]

5. Mechanism of Action for Prevention Remedy to Manage Lmphadenopathy

Inflammatory signals such as Type-1 interferons including IFN Alpha and IFN Beta [68] and omega are produced by many cell types including lymphocytes (NK cells,B cells and T cells),macrophages, endothelial cells, fibroblasts, osteoblasts and others which participate an anti-viral response as adapt immunity involving IRF 3/IRF 7 Anti -viral pathway and active against tumours.

IFN Alpha are found in all mammals and homologus species that presented in birds, reptiles, amphibians and fish species which bind with interferon receptor-opioid μ to act as an analgesic by producing plasmacytoid dendritic cells and exhibit circulation effect in blood as well as peripheral lymphoid organ in order to achieve adapt immunity against viral infection.

IFN beta and beta 1 are found in fibroblasts-connective tissue in animals which participate inhibition immune cell production of growth factors thereby stopping down tumour angiogenesis and hindering the tumour from connecting into blood vessel system .IFN beta 1 is used as a treatment for multiple sclerosis. [69]

Simultaneously these proteins are participated in synthesises extracellular matrix and collagen production helping to involve wound healing activity.

IFN ω is released by leucocytes at site of viral infection or turmeric which produces adaptive immunity effects.

Type 1 interferons -Annexin A2 a membrane forming protein encoded by ANXA 2 *gene* [70] helps to regulate Vomocytosis process and promote fusing of vesicles to plasma membranes.

Mechanism of action of vomocytosis-exocytosis action is one of rearrangements of actin (globular multi functional proteins) that form microfilaments in cytoskeleton and thin filaments in muscle fibrils which are found in eucaryotic cells. cytoskeleton is a complex, dynamic network of interlinking protein filaments present in cytoplasm of cells including bacteria and archaea.

Vomocytosis is the cellular process by phagocytes expel live organisms that they have engulfed without destroying the organism into external environment through rearrangement reaction. In contrast to standard exocytosis the engulfed pathogen is not lysed by internal components of the host cell and vesicle is brought close to cellular membrane where it can fuse and release pathogen cargo without undergoing rearrangement reaction.

Both the processess are enhanced by addition of weak bases to phagocytes instead of adding acidic. This process was reported at 2006 on the basis of time lapse microscopy footage characterising the interaction between macrophages and the human fungal pathogen Cryptococcus neoformans.

Subsequently this process has also been seen with other fungal pathogens such as candida albicans and candida krusei and mycobacterium marinum. [71]

Mycobacterium marinum is defined as a slow growing mycobacterium (SGM) belonging to the genus mycobacterium and phylum actinobacteria which can infect immunocompetent and immunocompromised hosts. It can cause interior and exterior part of human skin infections such as cellulitis, hand cellulitis, facial cellulitis, orbital cellulitis, erysipelas, Abscess, Anorectal abscess, Bartholin gland abscess, Scrotal abscess [72], Necrotizing soft tissue infections, Necrotizing fasciitis, Necrotizing myositis, sporotrichosis, lymphangitis, Folliculitis, Osteomyelitis, Deep venous thrombosis, Pyomyositis and purple glove syndrome.

The reason behind to inability to destroy host of microorganism especially who have strong immune power -CD4 cell more than >200 cells/mm3 but helps to expel organism into environment in alkaline condition. Primary on set of action occurs in lungs due to encapsulated yeast and oblique aerobic condition. Un failure treatment can lead to cause fungal meningitis and encephalitis when CD4 cell count automatically less than <200 cells/mm3. This infection is referred as secondary infection with AIDS patients. Final failure treatment can produce brain abscess [73] such as subdural effusion, cryptococcomas, Demantia, spinal cord lesion ,isolated cranial nerve lesion, and ischaemic stroke. This stage is attained due to cryptococcus species, candida species, mycobacterium amoebae as well as marinum. During fatal condition, weaken immune system can adapt host of microorganism as a intracellular pathogen and destroy immune power as well as insufficient oxygen flow exploring death condition when dephosphorylating and inactivating transcription factors happened in body. Finally, Vomocytosis can be decreased in Annexin A2 deficient lines through deactivaton of MAP2K5 pathway. Dead body can be destroyed within one hour in order to prevent spread of infection.

Mechanism of action of Phagocytosis-endocytosis action [74] 60takes place who have strong immunity CD4 cell more than >200 cells/mm3. During this process phagocytosis, Phagocytic cells include neutrophils, macrophages, eosinophils, monocytes, dendritic cells and B-Lymphocytes will helpful to discarding free microorganisms in the blood and tissue fluids. Infection or tissue injury stimulates mast cells, basophils and other cells to release vasodilators to initiate inflammatory response. Vasodilation results in increased capillary permeability, enabling phagocytic white blood cells such as neutrophils, monocytes and eosinophils as well as other leucocytes to enter the tissue around the injured site. The leucocytes are then chemotactically attracted to the area of infection. In other words, inflammation allows phagocytes to enter the tissue and go to the site of infection. Neutrophils are the first to appear and are later replaced by macrophage.

Lymph nodules are unencapsulated masses of lymphoid tissue containing fixed macrophages and ever changing populations of B-Lymphocytes and T-Lymphocytes that are located in the respiratory tract, liver and gastrointestinal tract. Organisms entering these systems can be phagocytosed by lymph node containing reticular fibres that support fixed macrophages and dendritic cells as well as circulaing B-Lymphocytes and T-Lymphocytes (including T4 and T8 Lymphocytes) to initiate adaptive immune response. The lymph eventually enters the circulatory system at the heart to maintain the fluid volume of the circulation.

In addition, Langerhans cells (immature dendritic cells) are located throughout the epithelium of the skin, respiratory tract and the gastro intestinal tract where in their immature form they are attached by long cytoplasmic processes. Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by pro inflammatory cytokines, the dendritic cells, the dendritic cells detach from the epithelium, enter lymph vessels and are carried to reginal lymphnodes. By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naïve T Lymphocytes located in the Cortex of the Lymph nodes.

The spleen contains many reticular cell-a type of fibroblast that synthesises collagen alpha 1 (III) and uses it to produce reticular fibers. This reticular fibers helps to hold up fixed macrophages and dendritic cells as well as ever changing populations of circulating B & T Lymphocytes. Blood carries microorganisms to the spleen where they are filtered out and phagocytosed by the macrophages and dendritic cells and presented to the circulating B Lymphocytes and T-Lymphocytes to initiate adaptive immune responses. There are also specialised macrophages and dendritic cells located in the brain (microglia), lungs (alveolar macrophages), Kidney (mesangial cells), bones(osteoclasts) and the gastro intestinal tract (peritoneal macrophages), Liver (Kupffer cells).

6. Pathway Related to ERK 5: [75,76]

ERK 5 participated in the MAPK signaling pathway that exchange information surface signals to cellular DNA was shown to slo don effect vomocytosis and increases Mitogen activated protein kinase T is an enzyme that in humans is encoded by MAPK 7 gene which is participated

in variety of cellular processes such as differentiation, proliferation, transcription regulation and development. MAP is cranked up by MAP2K5-mitogen activated protein kinase 5 and exhibit downstream signaling processes of various receptor molecules including receptor tyrosine kinases and G protein coupled receptor. This is helpful to regulate gene expression by phosphorylating and activating different transcription factors.

Rate of vomocytosis were decreased in Annexin A2 deficient cell lines through macrophage kinase inhibitors which is linked P13 kinase signaling molecule in macrophages and lymphocytes. P13kinase inhibitor evaluates a macrpphage targeted pan P13 kinase inhibitor designed to repolarise macrophages to a M1like phenotype and also decrease macrophage and myofibroblast contribution to fibrosis.

P38 MAP Kinase [77] has been extensively characterised as a master regulator of cytokine production such as IL10 in macrophages leading to tumour mediated immunosuppression due to dysregulated NF-Kappa B which facilitate oncogenes and impaired immunosurveillance due to abnormal activity relate with pathological stresses in several tissues that include neuronal, bone, lung, cardiac and skeletal tissues, fetal tissues and red blood cells and tend to cause mutation of protein activity which increases enzyme activity as well as producing fasciocapulohumeral muscular dystrophy.

PI3 kinase [78] is an important signalling molecule in macrophages and lymphocytes. Our preclinical PI3 Kinase inhibitor programme evaluates a macrophage-targeted pan-PI3 kinase inhibitor designed to repolarize macrophages to a M1-like phenotype and also decrease macrophage and myofibroblast contribution to fibrosis.

7. Conclusion

Lymphadenopathy is the grave health problem globally. Nearly 36 clan herbal plants are helpful for effective approach treatment of various types of lymphadenopathy.

Plants have scientifically proven to possess novel compounds with antimicrobial, antiprotozoal, antibacterial, antiviral, antiprotozoal and antimycocidal activity.

These list of herbal family is suitable for various immunologic and reticuloendothelial system disease conditions such as localized infections such as streptococcal pharyngitis, syphilis, infectious mononucleosis, hepatitis, fungal infections, toxoplasmosis, HIV.

Immunological reactions related with known antigens such as serum sickness, Immunological reactions related with unlabelled antigens such as sarcoidosis, connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus, Giant lymphnode hyperplasia, dermatopathies, lymphadenitis, immunoblastic lymphadenopathy. Lymphadenopathy are associated with benign medical problems to lifethreatening diseases such as malignant processes-Diffuse involvement such as lymphomas and leukemias. Diffuse invasion such as carcinomatosis, localized invasion such as head and neck tumors, lipid storage diseases and Graves addisons diseases.

Apart from herbal treatment, Lymphadenopathy can be cured via microbial symbiosis treatment in various conditions such as cancer, allergic immune disorders, metabolic Disorders and neurological disorders. Microbial symbiosis plays a greater role in long term biological interaction between two different biological organisms host (pathobionts) and microbial symbionts. The human symbiotic relationship can be expressed on the basis of beneficial factorial design such as commensalism-bacterial benefit, mutalism-Bacterial human benefit, Parasitism (human host harmed). Inorder to avoid, Dysbiosis in intestine (Imbalances in the bacterial composition), human gut microbiota modulates the host immune in a positive way via mutalism relationship (Both human-bacteria benefit).

Emphasis about Correlation factors in between IBD and Asthuma:

Short chain fatty acids such as acetate, butyrate and propionate–bye products of gut bacteria metabolism will tend to decrease allergic inflammation especially asthuma. In combination with short chain fatty acids and B-Complex vitamins will tend to decrease IBD inflammation.

The mechanism behind in inflammatory response is that short chain fatty acids metabolites produced by Acinetobacter, Bifidobacterium, Ruminococcus, streptococcus, staphylococcus, Enterococcus, Pseudomonas, Klebsiella, Proteus, E.coli, Faecalibacterium, Eubacterium and coprococcus which inhibit Histone deacetylases as well as GPCR signaling molecules. Further it downregulates Nuclear factor KB (NF-KB) and pro inflammatory Tumour necrosis factor (TNF) and exhibit antiinflammatory effects on macrophages and dentric cells.

Bacillus fragilis which acts as human symbiont prevents colitis by producing PSA polysaccharides A.PSA upregulate production of IL-10 and suppresses inflammation and decrease production of IL-17, TNF α and IL-23.

In order to activate inflammatory T cells and prevent colitis infection due to activation of mucosal immunity and intestinal microbiota, Treatment can be provided in combination of TNBS-Trinitrobenzene sulphonic acid and PAS. commensal bacteria regulate immune responses via stimulation of TLR4-Transmembrane protein pattern recognition receptor which inhibit allergic responses to food.

Hypothetical relationship hyper enhancement of C-Reactive protein in autoimmune diseases can be controlled by using Ah-Shi points Traditional Chinese medicine. The hyperenhancement of C-Reactive protein can be identified by psychogenic activity with emotional stress such as sudden onset, situational, morning erection positive, Rigidity of morning erection, other psychological compliants, spouse relationship and abnormal sexual development. This activity can be prevented b exercise such as walking, running, jumping, Hip-Hop, lifting, exercise, yoga and meditation.

In comparison with organic causative factor activity can be identified by gradual onset, morning erection negative, chronic medical illness, pelvis trauma/surgery, endocrine/neurological diseases, Recreational drugs, positive and negative loss of libido, +/-reduced size of penis. This can be prevented by involvement immune chemical reaction -antigen/antibody reaction using adjuvant therapy-vaccination enhancement of immune chemical reaction via healthy sexual partner, follow up

yoga poses, follow up nutrition chart inorder to maintain metabolic acidosis-metabolic alkalosis, Systematic apply reinforcing method towards Ah-Shi points even method technology through source points of kidney channel, liver channel, yin channel, large intestine channel and spleen channel.

References

[1] Harvey, AM, Bordley, J., 1972. Differential diagnosis, 361-64.

[2] Ashraf Kagee., Melvyn Freeman., 2017. In International Encyclopedia of Public Health (Second Edition).

[3] James, G.H., Dinulos, MD., 2021. in Habif's Clinical Dermatology.

[4] Nieuwenhuis, P., Opsteltew, D., 1984. Functional anatomy of germinal centers. Am J Anat, 170, 421-35.

[5] Vincent Chong., 2004. Cervical lymphadenopathy: what radiologists need to know, Cancer Imaging, 4(2), 116-120, 2004.

[6] Mohsin Sheraz Mughal., Rameez Rehman., Ramy Osman., Nathan Kan., Hasan Mirza., Margaret H Eng., 2020. Hilar lymphadenopathy, a novel finding in the setting of coronavirus disease (COVID-19): a case report. J Med Case Rep, 14(1), 124.

[7] Jessica K Staszak., Polina Zmijewski., Sandra Arnold., Bindiya Bagga., Regan F Williams., 2019. Mediastinal Lymphadenopathy in Children With Histoplasmosis. Journal of surgical research, 244, 558-565.

[8] Klotz, SA., Ianas, V., Elliott, SP.,2011. Cat-scratch Disease. American Family Physician, 83 (2), 152-155.

[9] Saifullah, MK., Sutradhar, S R., Khan, N A., Haque, M F., Hasan, S M ,Sumon, M Z., Islam, S Rahman., Barman, T K ., Rahman, A., Datta, P K., Ferdous, J., Chowdhury, S A., Miah, A H., Pandit, H., 2013. Diagnostic evaluation of supraclavicular lymphadenopathy. Mymensingh Med J, 22(1), 8-14.

[10] Mark R. Jones., Amit Prabhakar., Omar Viswanath., Ivan Urits., Jeremy B. Green. Julia B. Kendrick., Andrew J. Brunk., Matthew R. Eng., Vwaire Orhurhu., Elyse M. Cornett., Alan D. Kaye., 2019. Thoracic Outlet Syndrome: A Comprehensive Review of Pathophysiology, Diagnosis, and Treatment. Pain Ther,8: 5-18.

[11] Schroder, K. H., Juhlin, I., 1977. Mycobacterium malmoense sp. International Journal of Systematic Bacteriology, 27 (3), 241-246.

[12] Cheung, GY., Bae, JS., Otto, M., 2021. Pathogenicity and virulence of Staphylococcus aureus. Virulence, 12 (1), 547-569.

[13] Bhatia, A., Maisonneuve, JF., Persing, DH.,2004. Proprionibacterium acnes and Chronic Diseases.National Academies Press (US).

[14] Chanock,RM., Hayflick, L., Barile, MF.,1962. Growth on artificial medium of an agent associated with atypical pneumonia and its identification as a PPLO. Proceedings of the National Academy of Sciences of the United States of America, 48 (1), 41-9.

[15] Bentley, SD., Maiwald, M,, Murphy, L., Pallen, MJ., Yeats, CA., Dover, LG., Norbertczak, HT., Besra, GS., 2003, *Sequencing and analysis of the genome of the Whipple's disease bacterium Tropheryma whipplei. Lancet, 361 (9358)*, 637-44.

[16] Iván Posso-Osorio., Alejandra De Las Salas., Gabriel J Tobón Melibea Sierra-Ruiz ., Carlos A Cañas., Juan Carlos Bravo., Pablo A Moncada 2020, Mycobacterium malmoense: an unusual pathogen causing endocarditis, a case report and literature review. IDCases, 22.

[17] *Schroeder, Janice L., Steinke, Elaine E., 2005.* Necrotizing fasciitis--the importance of early diagnosis and debridement. The Association of peri Operative Registered Nurses, *82 (6)*, 1031-1040.

[18] Hoff, B. Fogle, B., 1970. *Case report. Histoplasmosis in a dog, Canadian Veterinary Journal, 11 (7)*, 145-148.

[19] Saunders, BM., Cooper, AM., 2000. Restraining mycobacteria: role of granulomas in mycobacterial infections. Immunology and Cell Biology, 78 (4), 334-41.

[20] Cole, AM., Tahk, S., Oren, A., Yoshioka, D., Kim, YH., Park, A., Ganz, T., 2001. Determinants of Staphylococcus aureus nasal carriage, Clinical and Diagnostic Laboratory. Immunology, 8 (6), 1064-1069.

[21] Whidbey, C., Harrell, MI., Burnside, K., Ngo, L., Becraft, AK., Iyer, LM., Aravind, L., Hitti, J., Waldorf, KM., Rajagopal, L., 2013. A hemolytic pigment of Group B Streptococcus allows bacterial penetration of human placenta. J Exp Med, 210 (6), 1265-1281.

[22] Doern., Christopher, D., Burnham., Carey-Ann D., 2010. It's Not Easy Being Green: the Viridans Group Streptococci, with a Focus on Pediatric Clinical Manifestations. Journal of Clinical Microbiology, 48 (11), 3829-3835.

[23] *Dekker, J. P., Lau, A. F., 2016.* An Update on the Streptococcus bovis Group: Classification, Identification, and Disease Associations. *Journal of Clinical Microbiology, 54 (7)*, 1694-1699.

[24] Euzéby, J.P., 1997. Firmicutes List of Prokaryotic names with Standing in Nomenclature *(LPSN).* International Journal of Systematic Bacteriology, 47, 590-592.

[25] Kouchak., Farideh Askarian., Mehrdad., 2012. Nosocomial Infections: The Definition Criteria. Iranian Journal of Medical Sciences, 37 (2), 72-73.

[26] Nilsson, Oskar., 2012. *Vancomycin resistant enterococci in farm animals – occurrence and importance Infection. Ecology & Epidemiology, 2, 16959.*

[27] Al-Abri, SS., Beeching, NJ., Nye, FJ., 2005. *Traveller's diarrhea. The Lancet. Infectious Diseases, 5 (6), 349-60.*

[28] Carlos E. Flores., Luís Loureiro., Lucinda J. Bessa., Paulo Martins da Costa., 2013. Presence of Multidrug-Resistant E. coli, Enterococcus spp. and Salmonella spp. in Lakes and Fountains of Porto, Portugal. Journal of Water Resource and Protection, 5(11).

[29] Niels Hoiby., Oana Ciofu., Thomas Bjarnsholt., Pseudomonas aeruginosa biofilms in cystic fibrosis. Future Microbiol, 5(11), 1663-74.

[30] Jing Yuan., Chen Chen., Jinghua Cui., Jing Lu., Chao Yan., Xiao Wei., Xiangna Zhao., NanNan Li., Shaoli Li., Guanhua Xue., Weiwei Cheng., Boxing Li., Huan Li., Weishi lin., Changyu Tian., Jiangtao Zhao., Juqiang Han., Daizhi An., Qiong Zhang., Hong Wei., Minghua Zheng., Xuejun Ma., Wei Li ., Xiao Chen., Zheng Zhang ., Hui Zeng .,Sun Ying.,JianXin Wu., Ruifu Yang., Di Liu., 2019, Fatty Liver Disease Caused by High-Alcohol-Producing Klebsiella pneumonia. Cell Metab, 30(4), 675-688. e7.

[31] Chen., Chi-Yu., Chen., Yen-Hsu, Lu., Po-Liang, Lin., Wei-Ru, Chen., Tun-Chieh., Lin., Chun-Yu., 2012. Proteus mirabilis urinary tract infection and bacteremia: Risk factors, clinical presentation, and outcomes, Journal of Microbiology. Immunology and Infection, 45 (3), 228-236.

[32] Mahesh Gajendran., Priyadarshini Loganathan., Guillermo Jimenez., Anthony P Catinella., Nathaniel Ng., Chandraprakash Umapathy., Nathalie Ziade., Jana G Hashash., 2019. A comprehensive review and update on ulcerative colitis. Disease a month, 65(12), 100851.

[33] Corbel, Michael., 1997. *Brucellosis: An Overview. Emerging Infectious Diseases, 3 (2)*, 213-21.

[34] Haitao Wang., Shanji Nan., Ying Wang., chengbi xu., 2021. CDX2 enhances natural killer cell–mediated immunotherapy against head and neck squamous cell carcinoma through up-regulating CXCL14. Journal of cellular and molecular medicine, 25(10), 4596-4607.

[35] Peeling, RW., Mabey, D., Kamb, ML., Chen, XS., Radolf, JD., Benzaken AS., 2017. *Syphilis. Nature Reviews. Disease Primers*, 3, 17073.

[36] Koichi, y., Arvin, AM., Campadelli-Fiume, G., Mocarski, E., Patrick, M., Roizman, B., Whitley, R., 2007. *Human Herpesviruses, Biology, Therapy and Immunoprophylaxis.* Cambridge University Press.

[37] Manns. M.P., 1997. Hepatotropic viruses and autoimmunity. 1997. J Viral Hepat. 4, 1, 7-10.

[38] Amon, W, Farrell, PJ., 2004. Reactivation of Epstein-Barr Virus from latency. Reviews in medical virology, 15(3), 149-56.

[39] Mahajan., Monika., 2021. Etymologia: Histoplasma capsulatum. Emerging Infectious Diseases, 27 (3), 969.

[40] Olender., Alina., 2013. The cause of Actinomyces canalictulis. Annals of Agricultural and Environmental Medicine, 20, 742-744.

[41] Ferry., Tristan., Valour., Florent., Karsenty., Judith, Breton., Pierre., Gleizal., Arnaud., Braun., Evelyne Chidiac., Christian., Ader., Florence., Senechal., Agathe., Dupieux., Celine Lustig., Sebastien., Boussel., Loic., Laurent., Frederic., 2014. Actinomycosis: etiology, clinical features, diagnosis, treatment, and management. Infection and Drug Resistance, 7, 183-197.

[42] Johnson, J L., Moore., Lillian, H., Kaneko., Beverly, Moore, W E C., 1990. Actinomyces georgiae sp.no., Actinomyces gerencseriae sp. nov., Designation of Two Genospecies of Actinomyces

naeslundii, an Inclusion of A. naes.undii serotypes II and III and Actinomyces viscosus serotype II and A. naeslundii Genospecies 2. *International Journal of Systematic Bacteriology, International Union of Microbiology Societies, 40 (3),* 273-286.

[43] Ford, BJ., 2005. The discovery of Giardia. The Microscope, 53 (4), 148-153.

[44] Buret, AG., 2008, Pathophysiology of enteric infections with Giardia duodenalius. Parasite, 15 (3), 261-5.

[45] Cotton, JA., Beatty, JK., Buret, AG., 2011,Host parasite interactions and pathophysiology in Giardia infections. International Journal for Parasitology, 41 (9), 925-33.

[46] Evans-Osses, Ingrid., Ansa-Addo., Ephraim, A., Inal, Jameel, M., Ramirez, Marcel, I., 2010, Involvement of lectin pathway activation in the complement killing of Giardia intestinalis. Biochemical and Biophysical Research Communications, 395 (3), 382-386.

[47] Tellez, Aleyda., Winiecka-krusnell, Jadwiga., Paniagua, Margarita., Linder, Ewert., 2003. Antibodies in Mother's Milk Protect Children Against Giardiasis. Scandinavian Journal of Infectious Diseases, 35 (5), 322-325.

[48] Steven, s.witkin., Evelyn Minis., Aikaterini Athanasiou., Julie Leizer., Iara, M., Linhares., 2017. Chlamydia trachomatis: the Persistent Pathogen. Clin Vaccine Immunol, 24(10).

[49] Yang, H., Yang, H., Li, Z., Liu,., Wang, W., He, ., Fan, F., Sun, Y., Liu, J., Li, Y., Zeng, X., 2018. Japanese encephalitis virus/yellow fever virus chimera is safe and confers full protection against yellow fever virus in intracerebrally challenged mice. Vaccine, 36(18): 2450-2455.

[50] *Samaranayake, LP.,2009. Essential microbiology for dentistry (3rd ed.), 178-180, 247, 293-297.*

[51] Klevens, R. Monina., Edwards, Jonathan R., Richards, Chesley L., Horan, Teresa C., Gaynes, Robert P., Pollock, Daniel A., Cardo, Denise M., 2007. Estimating Healthcare-associated Infections and Deaths in U.S. Hospitals, 2002. Public Health Reports, 122 (2), 160-166.

[52] Barry, MA., Weatherhead, JE., Hotez, PJ., Woc-Colburn, L., 2013, Childhood parasitic infections endemic to the United States. Pediatric Clinics of North America, 60 (2), 471-85.

[53] Chen, R., Zhang, M,., Li, Q., Xiong, H., Liu, S., Fang, W., Zhang, Q., Liu, Z., Xu, X., Jiang, Q.J., 2017, Retraction: The Epstein-Barr Virus-encoded miR-BART22 targets MAP3K5 to promote host cell proliferative and invasive abilities in nasopharyngeal carcinoma. Cancer, 8(16), 3130.

[54] Idris Nasir Abdullahi., Anka Abubakar., Anthony Uchenna Emeribe., Kabir Umar., 2021, The interplay between environmental factors, Vector Competence and vaccine immunodynamics as possible explanation of the 2019 Yellow fever Re-emergence in Nigeria. New Microbes and New Infections, 41.

[55] Whitehead, WE., Palsson, O., Jones, KR., 2002. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications?.Gastroenterology, 122 (4), 1140-56.

[56] Samuels .DS., Radolf JD Borrelia., Molecular Biology, Host Interaction and Pathogenesis. Caister Academic Press; 2010, 547.

[57] *Delmas, B., Attoui,H.,Ghosh, S., Malik, Y., Mundt, E., Vakharia, VN., 2019. Ictv Report, Consortium, ICTV virus taxonomy profile Birnaviridae. The Journal of General Virology, 100, 5-6.*

[58] Nobiron, I., Galloux, M., Henry, C., Torhy, C., Boudinot, P., Lejal, N., Da Costa, B., Delmas B., 2008. Genome and polypeptides characterization of Tellina virus 1 reveals a fifth genetic cluster in the Birnaviridae family. Virology, 371 (2), 350-61.

[59] Prashanth, G., Basavaraj Vastrad., Anandkumar Tengli., Chanabasayya Vastrad., Iranna Kottursheti., 2021. Investigation of candidate genes and mechanisms underlying obesity associated type 2 diabetes mellitus using bioinformatics analysis and screening of small drug molecules.BMC Endocr Disord, 21(1), 80.

[60] Kumar, B., Tripathi, C., Kanchan, RK., Tripathi, JK., Ghosh, JK., Ramachandran, R., Bhadauria, S., Tripathi, RK., 2013, Dynamics of physical interaction between HIV-1 Nef and ASK1: identifying the interacting motif(s). Plos one, 8(6), e67586.

[61] Kumar, A., Singh, UK., Kini, SG., Garg, V., Agrawal, S., Tomar, PK., Pathak, P., Chaudhary, A., Gupta, P., Malik, A., 2015, JNK pathway signaling: a novel and smarter therapeutic targets for various biological diseases. Future Med Chem, 7(15), 2065-86.

[62] Kumar, DT., Doss, CG., 2016. Investigating the Inhibitory Effect of Wortmannin in the Hotspot Mutation at Codon 1047 of PIK3CA Kinase Domain: A Molecular Docking and Molecular Dynamics Approach. Advances in Protein Chemistry and Structural Biology, 102, 267-9.

[63] Ishaq, M., Kumar, S., Varinli, H., Han, ZJ., Rider, AE., Evans, MD., Murphy, AB., Ostrikov, K., 2014, Atmospheric gas plasma-induced ROS production activates TNF-ASK1 pathway for the induction of melanoma cancer cell apoptosis. Mol Biol Cell, 25(9), 1523-31.

[64] Swaidani, S., Liu, C., Zhao, J., Bulek, K., Li, X., 2019. TRAF Regulation of IL-17 Cytokine Signaling. Front Immunol, 27, 10, 1293.

[65] Cui, J., Chen, Y., Wang, HY., Wang, RF., 2014. Mechanisms and pathways of innate immune activation and regulation in health and cancer. Hum Vaccin Immunother, 10(11), 3270-85.

[66] Dobrzycki, T., Lalwani, M., Telfer, C., Monteiro, R., Patient, R., 2020. The roles and controls of GATA factors in blood and cardiac development. IUBMB Life, 72(1), 39-44.

[67] Al-Jaber, H., Al-Mansoori, L., Elrayess, MA., 2021. GATA-3 as a Potential Therapeutic Target for Insulin Resistance and Type 2 Diabetes Mellitus. Curr Diabetes Rev, 17(2), 169-179.

[68] Lutfalla, G., Roeckel, N., Mogensen, KE., Mattei, MG., Uzé, G., 1990. Assignment of the human interferon-α receptor gene to chromosome 21q22.1 by in situ hybridization. Journal of Interferon Research, 10 (5), 515-7.

[69] Kieseier, BC., 2011. The mechanism of action of interferon-β in relapsing multiple sclerosis.CNS Drugs, 25 (6), 491-502.

[70] Woodham, A., Raff, AB., Raff, LM., Da Silva, DM., Yan, L., Skeate, JG., Wong, MK., Lin, YG., Kast, WM., 2014. *Inhibition of Langerhans cell maturation by human papillomavirus type 16: a novel role for the annexin A2 heterotetramer in immune suppression. Journal of Immunology, 192 (10),* 4748-57.

[71] Streit, M., Böhlen, LM., Hunziker, T., Zimmerli ,S.,Tscharner, GG., Nievergelt, H., Bodmer, T., Braathen, LR., 2006. Disseminated Mycobacterium marinum infection with extensive cutaneous eruption and bacteremia in an immunocompromised patient. Eur J Dermatol, 16(1), 79-83.

[72] *Marx, John A. Marx., 2014. Skin and Soft Tissue Infections. Rosen's emergency medicine: concepts and clinical practice, 137.*

[73] Chen, L., Liu, Z., Su, Y., Wang, D., Yin., BShu, B., Zhang, J., Zhu, X., Jia, C., 2017. Characterization of Mycobacterium marinum infections in zebrafish wounds and sinus tracts. Wound Repair Regen, 25(3), 536-540.

[74] Gordon., Siamon., 2016. Phagocytosis: An Immunobiologic Process. *Immunity, 44 (3),* 463-475.

[75] Rupesh, K P., Moushumi Priya,A., Prashanth, K., Jayachandran. S., 2012. Inhibitory effects of bioactive leads isolated from Pseudomonas aeruginosa PS3 and Pseudomonas fluorescens PS7 on MAP kinases and down regulation of pro inflammatory cytokines (TNF-α, IL-1β) and mediators (NO, iNOS and COX), Toxicol In Vitro, 26(4), 571-8.

[76] Rupesh Paudel., Lorenza Fusi., Marc Schmidt., 2021, The MEK5/ERK5 Pathway in Health and Disease. Int J Mol Sci, 22(14), 7594.

[77] Segalés, J., Perdiguero, E., Muñoz-Cánoves, P., 2016. Regulation of Muscle Stem Cell Functions: A Focus on the p38 MAPK Signaling Pathway Frontiers in Cell and Developmental Biology, 4, 91.

[78] Kumar, DT., Doss, CG., 2016. Investigating the Inhibitory Effect of Wortmannin in the Hotspot Mutation at Codon 1047 of PIK3CA Kinase Domain: A Molecular Docking and Molecular Dynamics Approach. Advances in Protein Chemistry and Structural Biology, 102, 267-9.