ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

HARNESSING THE POWER OF HERBAL IMMUNOMODULATORS: A COMPREHENSIVE REVIEW

Ravi Kumar [1*], Rani Kumari[1], Aditi Chaudhary[2], Arpita Choudhary[2], Jagat Pal Yadav[3], Shubhrat Maheshwari[4], Neeraj Jain[5], Neelam Jain[6]

[1]Narayan institute of pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, Bihar-821305

[2]Faculty of Pharmaceutical Sciences, Rama University, Mandhana, Kanpur (U.P.) India-209217

[3]Department of Pharmacology, Kamla Nehru Institute of Management and Technology, Faridipur, Sultanpur, Uttar Pradesh 228118, India

[4]Rajarshi Rananjay Sinh College of Pharmacy, Amethi, Uttar Pradesh 227405, India

[5]Teerthankar Mahaveer College of Pharmacy, TMU, Moradabad U.P.

[6]Faculty of Pharmacy, Oriental University, Indore, M.P, India

***Corresponding author:** Ravi Kumar**,** Narayan institute of pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, Bihar-821305

(Email id – ravi09784@gmail.com)

Abstract: The use of herbal immunomodulators has gained considerable attention in recent years owing to their potential in enhancing the body's immune response and maintaining overall health. This review paper aims to provide a comprehensive overview of various herbal immunomodulators, their mechanisms of action, and their therapeutic applications. We discuss the scientific evidence supporting the efficacy and safety of these botanicals, their traditional uses, as well as ongoing research and future perspectives in this burgeoning field.

Keywords: Antigen Presenting Cell, Deoxyribonucleic Acid, Interferon(Chemokine), Interleukin(Chemokine), Inducible Nitric Oxide Synthase,Minimum Inhibitory Concentration

1.1 IMMUNE SYSTEM

An immune system is a system of biological structures and processes within an organism that protect against disease by identifying and killing pathogens and tumours cells.It detects a wide variety of agents ,from viruses healthy cells and tissues in order to function properly . detection is complicated as pathogens can evelve rapidly ,producing t avoid immune system and allow the pathogens to successfully infect their host[1.]

To survivethis challenge ,multiple mechanisms evolved that recognize and neutralize pathogens . even simple unicellular organisms such as bacteria possess enzymes system that protect against viral infections other basic immune mechansism evolved in ancient eukaryotes and remain in their modern descendants ,such as plants ,fish,reptiles,and insects . these meschanisms include antimicrobial peptides called defenses,phagocytosis,and the complement system .vertebrates such as humans have even more

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

sophesticates defence system . the immune system of vertebrates consists of many types of proteins , cells, organs, and tissues , which interact in an elaborate and dynamic network . As part of this complex immune response , the human immune system adapts over time to recognize specific pathogens more efficiently .this adaptation process is reffered to as “adaptive immunity” or “acquired immunity” and creates immunological memory . immunological memory created from a primary response to a specific pathogens ,provides an enhanced response to secondary encounters with that same , specific pathogens . This process of acquired immunity is the basis of vaccination[2] .

Disorders in the immune system can result in disease . immunodefficiency occureswhen the immune system is less active than normal , resulting in reoccurring and life threatening infections . immunodeficiency can eitherbe a result of genetic disease , such as severe combined immunodeficiency , or be produced by pharmaceuticals or an infections such as the acquired immuno deficiency syndrome (AIDS) that is caused by the retrovirus HIV. In contrast , autoimmune diseses include hashimoto’s thyroiditis, rheumatoid arthritis ,diabetes mellitus type 1 and lupus erythematosus. Immunology covers the study of all aspects of the immune system which has significant relevance to human health and diseases.further investigation in this field is expected to lay a serious role in promotion of health and treatment of diseases[3].

1.2 PHYSIOLOGICAL REGULATION

Hormones can act as immunomodualtors , altering the sensitivity of the immune system. For example, female sex hormones are known immunostimulators of both adaptive and innate immune responses. Some autoimmune diseases such as lupus erytgematosus strike women prefentially , and their onset often coincides with puberty. By contrast, male sex hormones such as testosterone seem to be immunosuppressive. other hormones appear to regulate the immune system as well , most notably prolactin , growth hormone and vitamin D . It is conjectured that a progressive decline in hormone level with age is partially responsible for weakened immune responses in aging individuals. Conversely, some hormones are regulated by the immune system notably thyroid hormones activity[4].

1.2.1 SLEEP ;

The immune system is enhanced by sleep and rest and is impaired by stress. sleep deprivation is determental to immune function , and sleep can be considered a vital part of the immune system. Viewed in this light, decrease in the length and quality of sleep in the population has far reaching public health implications. complex feedback loops exist between the sleep cycle and immune response ; acute –infection causes changes in the sleep cycle including an increase in slow wave sleep relativeto rem sleep . cytokines , a class of peptides ,appear to be one of the main mechanisms through which the immune system and sleep cycle interact,as cytokines are produced by the immune system in response to infection,and also plays a role in the normal sleep cycle .

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

1.2.2 Nutrition and Diet;

The functioning of the immune system ,like most system in the body ,is dependent on proper nutrition .it has been long known that severe malnutrition leads to immunodefficiency .overnutrition is also associated with diseases such as diabetes and obesity which are known to affect immune function .more moderate malnutrition ,as well as certain specific trace minerals and nutrients deficiencies ,can also compromise the immune response .

Specific foods may also affect the immune system ;for example , fresh fruits,vegetables,and foods rich in certain fattyacids My foster a healthy immune system like wise ,fetal under nourishment can cause a lifelong impairment of the immune system.In traditional medicines ,some herbs arebelived to stimulate the immune system ,such as licorice ,ginseng,astragalus,elderberry,as well as honey.

Medicinal mushrooms like shiitake and maitake have shown evidence of immune system up regulation in vitro ,invivo,as well as in people.an isolated compounds from shiitake ,known as active hexose correlated compound has also shown evidence of being able to upregulate certain aspects of immune system .research suggest that the compound in the medicinal mushrooms are most responsible for upregulating the immune system and are a diverse collection of polysaccharides, particularly betaglucans ,and to a lesser extent ,alpha glucans .specifically beta glucans have the potential to stimulate the innate branch of immune system.the mechanism in which beta glucans are able to activate the immune system , is by interacting with the macrophage –I antigen (CD18) receptor on immune cells .other human receptors have been identified as being able to receive signals from beta glucans such as toll like receptors ,dectin-1,ect[5].

Published research has suggested that certain herbs can stimulate aspects of the immune system ,although further research is often needed to discover their mode of action.

1.3 **MANIPULATION IN MEDICINE**;

The immune response can be manipulated to suppress unwanted responses resulting from autoimmunity, allergy and transplant rejections, and to stimulate protective responses against that largely include the immune system (see immunization). Immunosuppressive drugs are used to control autoimmune disorders or inflammation when excessive tissue damage occurs and to prevent transplant rejections after an organ transplant.

Anti-inflamatory drugs are often used to control the effects of inflammation. The glucocorticoids are the most powerfull ofthese drugs ;however these drugs can have many undesirable side effects (e.g; central obesity , hyperglycemia,osteoporosis) and their use must be tightly controlled . therefore,lower doses of anti-inflammatory drugs are often used in conjunction with cytotoxic or immunosuppressive drugs such as methotrexate or azathioprine. Cytotoxic drugs inhibit the immune response by killing dividing cells such as activated T cells. However ,the killing is indiscriminate which causes toxic side effects. Immunosuppressive drugs such as ciclosporin prevent Tcells from responding to signals correctly by inhibiting signal transduction pathways [6].

High molecular weightdrugs (>500 Da) can provoke a neutralizing immune response ,particularly if the drugs are administerd repeatedly ,or in larger doses. This limits the effectiveness of drug based on larger peptides and proteins (wich are repeatedly larger than 6000 Da). In some cases the drugs itself is not

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

immunogenic but may be co administered with an immunologic compounds as is sometime the case of taxol. Computational meathods have been developed to predict the immunogenicity of peptides and proteins ,which are particularly usefull in designing therapeutic antibodies assessing likely virulence of mutation in viral coat particles,and validation of proposed peptide based drug treatments. Early technique relied mainly on observation that hydrophilic amino acids are overpresented in epitope regionsthan hydrophobic amino acids. However more recent developments rely on machine learning techniques using databases of existing known epitopes usually well studied viruses proteins as a training set. A publically axxesible database has been estabilised for the cataloguing of epitopes from pathogens known to be recognizable by B cells . the emerging field of bioinformatics based studies of immunologenicity is reffered to as immunoinformatics.

1.4 MANIPULATION BY PATHOGENS

The success of any pathogen is dependent on its ability to elude host immune responses. Therefore ,pathogens have developed several meathods that aloow them to successfully infect a host ,while evading detection or destruction by the immune system .bacteria often overcome physical barriers by secreating enzymes that digest the barrier for example – by using a type ii secreation system.

Alternatively using a type iii secreation system ,they may insert a hollow tube into a host cell,providing a direct route for proteins to move from pathogens to the host . these proteins are often used to shutdown host-defence[7].

An evasion strategy used by several pathogens to avoid the innate immune system is to hide within the cells of their host (also called interacellular pathogenesis).here a pathogen spent most of its lifecycle inside host cells where it is shielded from direct contact with immune cells,antibodies and complement some examples of intracellular pathogens include viruses , the food poisiong bacterium salmonella and the eukaryotic parasites that causes malaria(plasmodium falciparum) and leishmaniasis. Other bacteria , such as mycobacterium tuberculosis live inside a protective capsule that prevent lysis by complement many pathogens secrete compounds that diminish or misdirect the hosts immune response , some bacteria form biofilm toprotect themselves from the cells and proteins of the immune system. Such biofilms are mainly present in succesfull infections , eg; the chronic pseudomonas aeruginosa and burkholderia cenocepacia infections characteristic of cystic fibrosis .other bacteria generate surface proteins that bind to antibodies , rendering them ineffective ; examples include streptococcus (protein G),staphylococcus aureus (protein A) .
The mechanism used to evade the adaptive immune system are more complicated. The simplest approach is to rapidly change nonessentialepityomes (amino acid or sugars)on the surface of the pathogens while keeping essential epitopes concealed. This is called antigenic variation . an example is HIV ,which mutates rapidly , so the proteins on its vial envelop that are essential for entery into its host target cell are constantly changing . these frequent ,changes in antigens may explain the failure of vaccines directed at this virus. The parasite typnosoma brucei uses a similar startgy, constantly swiching one type of surface protein for another , allowingit to stay one step ahead of the antibody reponse . masking antigen with host molecules is another common streatgyfor avoiding detection by the immune systems. In HIV the envelop that covers the viron is formed from the outermost membrane of the host cell such"self cloaked"
Viruses make it difficult it difficult for the immune systemto identify them as non self structures[8].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

1.5 History Of Immunology

Immunology is a science that examines the structure and function of theimmune system. It originates from medicines and early studies on the causes of immunity to disease.the earliest known mention of immunity was during the plague of Athens BC. Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick withoutcontracting the illness a second time. In the 18 century , pierre-louis moreau in an experiment with scorpion venom and observed that certain dogs and mice were immune to this venom. This and other observations of acquired immunity later exploited by louis pasturein his development of vaccination and he proposed germ theory of disease. Pasture theory was in direct opposition to contemporary theories of disease, such as the miasma theory. It was not until Robert Koch's 1891 proofs for which he was awarded a nobel prize in 1905 that microorganism were confirmed as human pathogens in 1901,with discovery of the yellow fever viruses by waiter reed.

Immunology made a great advance towards the endof th 19th century , through rapid developments in the study of humoral immunity and cellular immunity. Particulary important was the work of paul ehrlich, who proposed the side chain theory to explain the specificity of theantigen antibody reaction ; his contribution to the understating of humoral immunity were recognized by the award of a nobal prize in 1908,which was jointly awarded to founder of cellular immunology,Elie Metchnikoff[9].

The world we live in is full of microbes. Our body temperature and wealth provides an ideal home for these microorganisms. The human immune system has the essential function of protecting the bodies against the damaging effects of microbial agents that are pathogenic. The symptoms comprises innate (non specific) and acquired(specific) immunity. Natural killer(NK) cells,complement system,macrophages,antigen presenting cells(APCs)and nutropihiles makeup the innate immune system,and mount an immediate non specific response to foreign microbial agenmts.if microbes by pass this primary defence the acquired immune response , comprising humoral and cell mediated components , will then act to contain the invaders.

The type of antigen (fungi, viruses,bacteria,toxins) processed and presented by APCs to the CD4+T cells determines the typeof cytokines secreted,which in turn,determine the differentiation of helper T(TH)cells into TH1 or TH2 cells and B-cellsto give immunoglobin subtypes. TH1 responses involves the activation of macrophages,which contain and destroy mycobacteria and fungal pathogens. TH1 pathway also activates cellmediated immunity.TH2 cells,on the other hand,effect immunoglobulin differentiation and antibody secreation and therefore mediate humoral immunity.

2.1.Traditional Chinese Medicine:

The concepts relating to traditional Chinese medicine (TCM) had already been well accepted by their practitioners ,when scientific proof of medical concepts emerged. For instance, the theory that blood circulates in the body, and is not static originated more than one thousand years before William Harvey described it in 1628. TCM incompasses 4 disciplines of practice: herbalism ,food cures ,acupuncture 1420 current medicinal chemistry,2004,volume 11, number 11 tan and vanitha[14].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

3. Immunomodulators

Medical treatment for crohn's disease and ulcerative colitis has two main goals : achieving reemission (the absence of symptoms) and once that is accomplished , maintaining remission (preventation of flare-ups). To accomplish these goals treatment is aimed atcontrolling the ungoing inflammation in the intesteine-the cause of IBD symptoms

As their name implies, immunomodulators weaken or modulate the activity of immune system. That, in term, decreases the inflammatory response. Immunomodulators are most often used in organ transplantation to prevent rejection of the new organ, and in autoimmune diseases such as rheumatoid arthritis.since the late 1960s the have also been used to treat people with IBD , which appears to be caused by an overactive immune system. These drugs are appropriate for those who ;

- Do not respond toamino salisylates,antibiotics, or corticosteroids
- Have steroid-dependent disease or frequently require steroids
- Have experienced side effects with corticosteroid treatment
- Have perineal disease that does not respond to antibiotics
- Have fistulas(abnormal channels between two loops of intestine,or between the intestine and another structure – such as the skin)
- Need to maintain remmision

An immunomodulator may be combined with a corticosteroid to speed up response during active flares of disease. Lower doses of steroids are required in these case,producing fewer side effects. Corticosteroids may also may be withdrawn more rapidly when combined with immunomodulators. For that reason, immunomodulators are sometimes reffered to as "steroid spairing" drugs[10].

3.1 Oral Medications:

The first two immunomodulators to be used widely in IBD are azathioprine and 6-mercaptopurine drugs that are chemically quite similar. They are used to maintain remission in crohn's disease and ulcerative colitis. Both have a slow onset of action(3-6 months for full effects).

Accordingly , they are usually given along with another faster-acting drug(such as corticosteroids). Other immunomodulators to treat IBD are cyclosporine A and tacrolimus,both used for organ transplaion as well. Cyclosporine A has more rapid onste of action (1-2 weeks) than azathioprine and 6-MP. It is usesfull in people with active crohn's disease ,but only when given interavanously and at high doses. Both cyclosporine A and tacrolimus have been more effective in treating people with severe ulcerative colitis and,are generally given until one of the slower- acting immunomodulators begins to work or until the patient undergoes curative surgery. Tacrolimmus can be used in crohn's disease when corticosteroids are not effective or when fistulas develop[11].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

3.2 Alternate Meathod Of Delivery:

Tacrolimus may be applied topically for crohn's disease that affects the mouth or perineal area. Topical tacrolimus is also used to treat pyoderma gangrenosum, an ulcerating skin disorder often associated with IBD. Methotrexate (MTX @,RHEUMATREX @,MEXATE @) woks more rapidly than azathioprine or 6-MP, and is given by weekly injections. It is an effective option for people with crohn's disease who have not responded to other treatments and cannot tolerate other immunosuppresents's. the effectiveness of methotrexate in ulcerativecolitis is as yet unproven.

3.3 Side Effects

- Azathioprine to 6-MP:- infrequently reported side effects may include headache,nausea,vomiting, diarrhea,and malaise,(general feeling of illness). Sometimes changing from azathioprine to 6-MP or viceversa may reduce some of these reactions. Canker sores in the mouth,rash, fever,joint pain and and lever inflammation are unlikely to be affected by changing from azathioprine to 6-MP or vice versa. Less common side effects include pancreatits (inflammation of the pancrease) and bone marrow suppression which may increase the risk of infection or serious bleeding. A return to normal blood cell production may take several weeks after discontinuing the medication.
- Cyclosporine and tacrolimus: in frequenly reported side effects include decreased kidney function hepatits, increased risk of infections,diabetes,increased cholesterol levels, sleep problems,headache,mild tremor,high blood preasure ,swollen gums, tingling of the fingures and feet, increased facial hairs,and increased risk of lymphoma (cancer of the lymphatic system).
- Ethotrexate: in frequently reported side effects include flu-like symptoms (nausea,vomiting,head ache ,faique and diarrhea) and low white blood cell count. Less common but more serious side effects include scarrinng of theliver and lung inflammation. Scaring of the liver can be made worse by diabeties,being overweight and alcohol consumption[12].

4. Drug Interactions :

People taking several different medicines, whether priscription or over the counter, should always be on the look out for interaction between drugs. Drug interactions may decrease a medication's effectiveness , intensify the action of drug ,or cause unexpected side effects. Before taking any medication,read the label carefully. Be sure to tell your doctor about all the drugs you are taking (even over- the –counter medications or complementary thearapies) and any medical condition you may have. A contemporary example of drug interaction used as an advantage is the co-administration of carbidopa with levodopa(available as carbidopa/levodopa). Levodopa is used in the management of parkinson's disease and must reach the brain in an un-metabolized state to be benificial. When given by itself levodopa is metabolized in the peripheral tissues outside the brain, which deacreases the effectiveness of the drug and increases the risk of adverse effects. However , since carbidopa inhibits the peripheral

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

metabolism of levodopa,the co-administration of carbidopa with levodopa allows more levodopa to reach the brain in unmetabolized and also reduces the risk of side effects.

Drug interaction may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drugs, such as alteration in the Absorbtion,distribution,metabolism and excretion(ADME) of a drug. Alternatively, drug interaction may the result of the pharmacodynamic properties of the drug,example is the coadministration pf a receptor antagonist and an agonist for the same receptor.

Metabolic Drug Interactions: Many drug interactions are due to alteration in drug metabolism. Further human drug metabolizing enzymes are typically activated through engagement of nuclear receptors[13].

One notable system involved in metabolic drug interactions is the enzyme system comprising the cytochrome P 450 oxidases. This system may be affected by either enzyme induction or enzyme inhibition, as discuss in the examples below:

- Enzyme induction- drug A induces the body to produce more of an enzyme which metabolises drug B. this reduces the effective concentration of drug B, which may lead to loss of effectiveness of drug B. drug A effectiveness is not altered
- Enzyme inhibition- drug A inhibits the production of enzyme metabolizing drug B, thus an elevation of drug B occurs possibly leading to an over dose
- Bioavailability- drug A influences the absobtion of drug B

5. Special Consideration:

- Immunomodulators reduce the activity of the immune system. In so doing they also decrease the body's ability to combart infection. Be sure to report any incidence of fever, chills or sore throat to your doctor
- Blood test should be performed frequently with all immunomodulators to check for effects on the bone marrow, liver and kidneys. blood pressure and kidney function need to be closely monitored with cyclosporine A and tacrolimus
- Women who are pregnant are wish to become pregnant should talk to their doctors before taking immunomodulators. Methotrexate use should be avoided(by pregnant women and by both men and women for several months before conception) because it may lead to pregnancy loss or possible birth defects

6. Summary Of Phytopharmaceuticals And Their Effects On Immune Cell:

1. Aloe vera leaves CARN750 pollysaccharide selectively stimulates cytokines, activates lymphocytes
2. Angelica dahurica roots 5,8-di(2,3-dihydroxy-3-methylbutoxy)-psoralen furocoumarins toxic to aspercillus candidus(R)-heraclenol furocumarins toxic to bacillus subtilis ferulic acid,Byakanelicin furocoumarins toxic to cladosporium herbarum, Angelica gigas roots Angelan polysaccharides selectively modulates cytokines
3. Astragalus membranaceus roots polysaccharides increase machrophage count soluble extracts selectively stimulates cytokines

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

4. Ganoderma lucidem fruting bodies wter soluble extract glycoprotiens selectively stimulates cytokinins GLIS proteoglycans stimulates lymphocytes water and ethanol soluble extract polysaccharides increase natural killer cell count,5 panax notoginseng roots penanotin peptide toxic tocoprinus comatus, physalospora piricola, botryts cinerea,fusarium oxysporum panaxagin peptide fungal ribosome inactivating protein
5. Panax ginseng roots panaxa diol, panaxa triols saponins stimulates lymphocytes and cytokines Ginsan acidic polysaccharide stimulates IL-1,IL-12,TNF and IFN Rhamnogalacturonan II saponins IL-6 stimulants
   Panax ginseng leaves Rhamnogalacturonan II saponins enhance macrophage actions stimulatesIL-6 activity
6. scutellaria barbata_roots apigenin flavonoid toxic to MRSA scutellaria biacalensis wogonin flavanoid stimulates TNF-_alpha , activates iNOS scutellari albida linalool flavonoid toxic to S.aureus,B.subtilis,E.coli and P.aeruginosa
7. Gingiber officinale rhizome citral antimicrobial[15].

1.Curcumin:_sasquiterpene__toxic to rhizoctonia solani dehydrozingerone___antifungal. 1,7-bis(4-hydroxy-3-methoxyphenyl)hept-4-en-3-one.schogasulphonic acid toxic to piricullaria oryzae ethanol soluble extract IL-1,IL-6 stimulant and manipulative thearapy. In this review, we focus on the herbal component of TCM[16].

The use of Chinese herbs is believed to have originated during the Xia dynasty ,more than 4000 years ago. The founder of Chinese medicine,shen nung, is regarded as father of medicines unlike many breakthroughs in drug discovery that came through serendipity such as discovery of penicillin and digoxin, it is belived that the discobery of the medicinal value of chines medicinal herbs was not by chance. History record that shen nung sampled plants in the hundreads to examine their effects , both good and bad. With the accumulation of medica ”is said to be the first book that summarized the properties and functions of over 300herbs. As communication linked improved , cultural exchanges between neighbouring nations ,korea, japan and india , brought about more plants with nutritional value and more ways to treat diseases

The concepts of Qi,Yin and yang,and the five elements in Chinese medicine,subsequently evolvwd to comprise ideas that climates (wind,cold,summer,hit,dampness,dryness and fire)and emotions(joy,anger,anxiety,terror)influence bodily disorientations.in later years,the concept that,”if there were no pathogens,there would be no diseases”some traditional Chinese medicinal herbs current medicinal chemistry,2004,vol.11,no11 1425 emerged.such was the foundation for the established fact that disease enters through opening in the body and that treatment og disease should be targeted at combating the pathogens[17].

A search of the literature reveled seven TCM herbs have been studied in some details for their immunomodulatory and antimicrobial effects. These herbs are also commonly used byTCM practitioners here in Singapore._This review also examinesin greater detail the studies done with specific phytochemicals and their effects on some biochemical parameters of the immune system.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

2.Aloe Vera: four vegetables are indispensible for the well being of man: wheat, the grape, the olive,and the aloe. The first nourishes him,the second raises his spirit,the third brings him harmony and the furth cures him – christopher coloumbus.

Fig.2.1

the aloe vera, originated from Africa,was introduced to china through the silk road. The plant become a treasured herb by the seventh century. Containing major constituents such as aloin, cocumaric acid,aldopentose,calcium oxlate and pollysacharides, aloe vera is a common element in cosmetic products

While raw leaf juice was traditionally used as laxatives , its mucilaginous gel is casually used to treat burns and cuts. The antimicrobial activity of aloe extracts was postulated as early as 1939.

Isolates from aloe vera were shown to inhibit microbes like staphylococcus sp. And candida sp. Clinical studies have revealed several immunomodulatory properties stronger leucocyte infilteration was seen in injured areas were aloe extract were used in treatment and surface wound recovery was stimulated by polyuronic acids[18].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

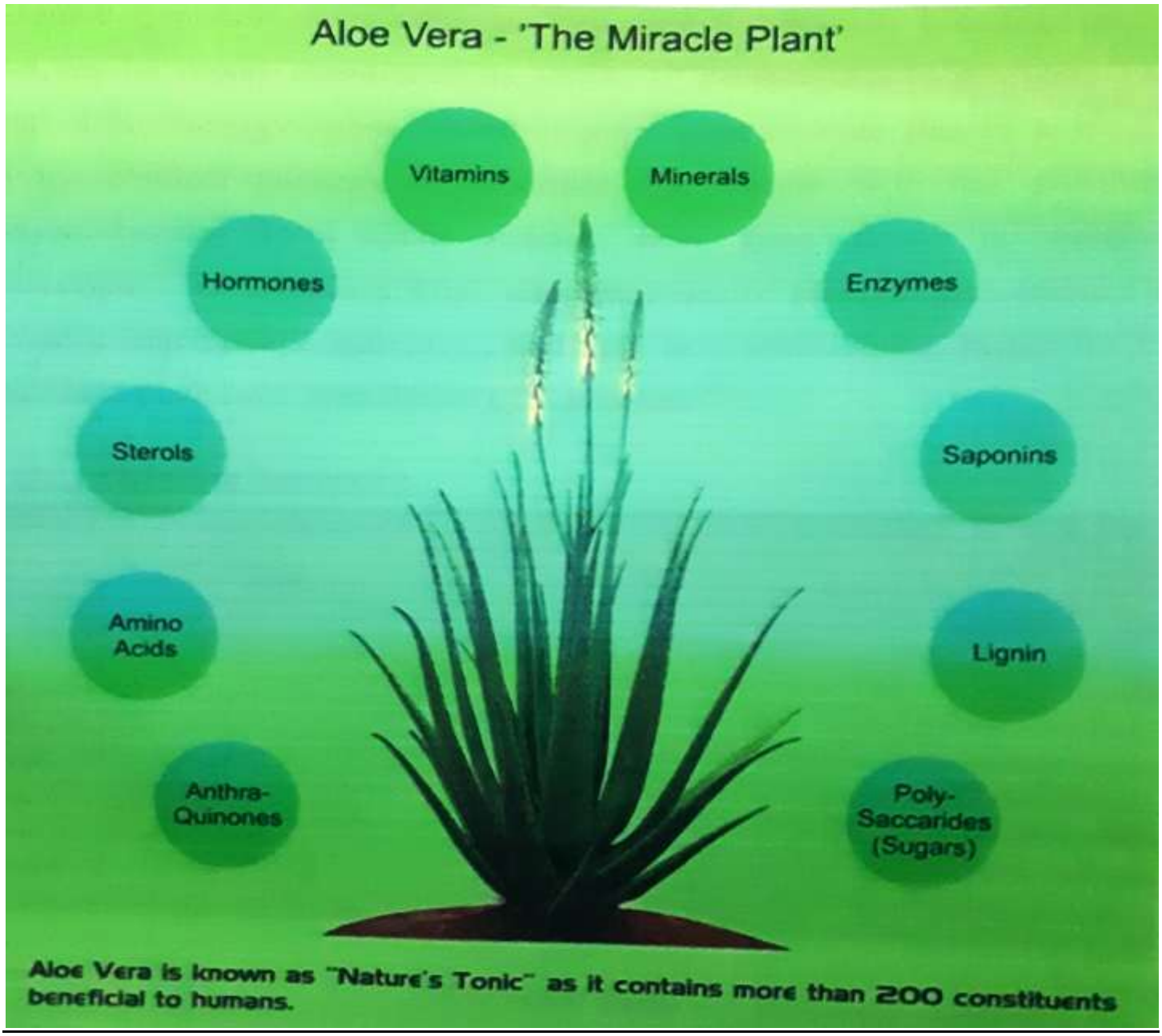


Fig.2.2

Acemannan ,the major fraction of aloe polysaccharides, has been extensively studied for immunomodulatory effects. Reports showed that these (1,4)-linked acetylated mannans areable to increase phagocytic activities CARN 750, an acemannan,stimulated leucocytes and lymphocytes in a dose-dependent manner,as well as triggered the release of IL-1,IL-6 and TNF- administrations of CARN-750 also showed a positive influence on lymphocyte proliferation in the spleen and bone marrow, both of which are essential lymphoid organs that produce and differentiate lymphocytes. In fact, earlier reprts mentioned the ability of acemannans to stimulate TH2 cells. It has been postulated that the actions of acemannans may be attributed to the residual presence of

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

aloerides. In accord with this postulated, polysaccharides from crude extracts have been shown to enhance transcription of cytokines. High concentrations of aloerides also seemed to enhance macrophage activities, and may be a contributing factor for the increased phagocyte stimulation by the acemannans[19].

Marketed Products; Suwasthi Fibrous Aloevera Juice,Kapiva Aloevera Juice,Sovam Aloevera Juice Etc.

3.Tulsi(Ocimum Sanctum):

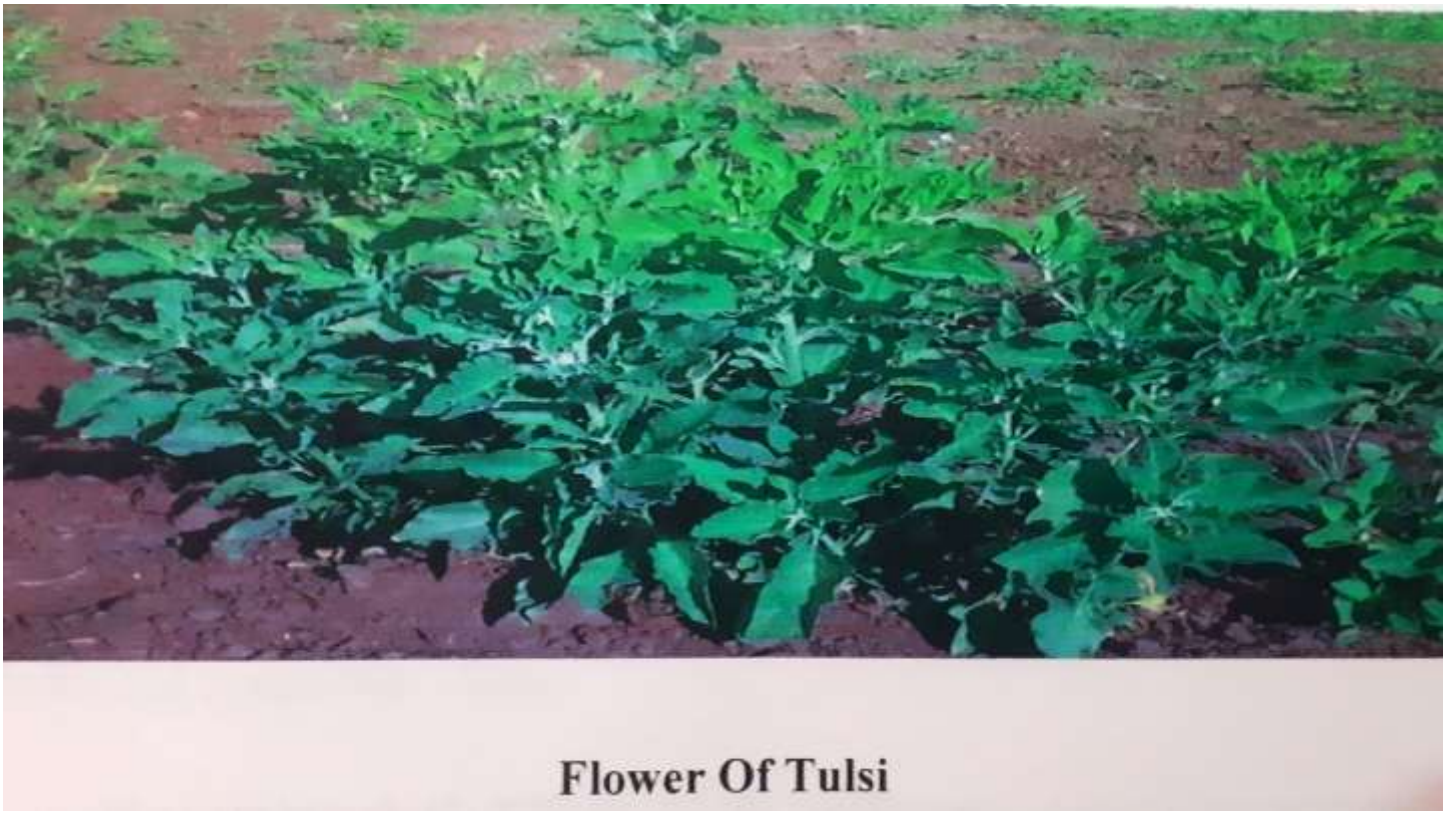


Fig.3.1

OCIMUM SANCTUM(holly basil),called tulsi in india, is ubiquitous in hindu tradition.

Perhabes its role as a healing herb was instrumental in its “sacred” implication. Ocimum sanctum (tulsi)is perhaps the most common and most revered of all house hold plants in india.

Tulsi is an erect sweet scented pubescent herb,32-100 cm in height, growing in abundance in near cultivated field and gardens and waste lands its leafs , seeds and whole plant is usefull[20].

PROPERTIES;- Rasa-katu(sharp) tikta(bitter, virya-ushna(hot),vipak-katu(sharp).

Ayurvedic practice recommends tulsi in several formulations to enhance i9mmunity and metabolic functions as well as in the management of respiratory problems (shawas-kasa)[21].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

Chemical constituents;- a verity of biologically active compounds have been isolated from the leaves including ursolic acid, apigenin and leuteolin

Fig.3.2

Medicinal Properties/Uses;-

- Pharmacological effects- in traditional ayurvedic systems of meidicines several medicinal properties have been attributed to this plant. Recent pharmacological studies have established the anabolic, hypoglycemic,smooth muscle relaxant, cardiac depressants ,antifertility,adaptogenic and immunomodulator properties of these plants
- Antimicrobial effects- essential oil of tulsi have antibacterial and antiviral properties it inhibits the growth of E.coli,B.anthracis,M.tuberculosis etc. its antitubercular activity is one-tenth the potency of streptomycin and one- fourth that of isoniazid. Preparations containing tulsi extraxt significantly shorten the course of illness,clinical symptoms and the biochemical parameters in patients with viral hepatitis and viral encephalitis[22].
- Antimalarial effects;- essential oil of tulsi have been reported to possess 100% larvicidal activity against the culex mosquitoes. Trials have shown excellent antimalarial acivity of tulsi.its extract have marked insecticidal activity against mosquitoes. Its repellent action last for about two hours.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

- Antiallergic and immunomodulator effects;- essential oil of tulsi was found to have antiallergic properties. When administered to laboratory animals, the compound was found to inhibit must cell degranulation and histamine release in the presence of allergen. These studies revele the potential role of ocimum sanctum extracts in the management of immunological disorders including allergies and asthma.
- Antistress/adaptogenic effects;- extract from the plant have been found to reduce stress.
- Antifertility effect;- one of the major constituents of the leaves, ursolic acid has been reported to possess antifertility activity in rats and mice, this effect has been attributed to its anti-estrogenic effect which may be responsible for arrest of spermatogensis in males and inhibitory effect on implantation of ovum in females. These constituents may prove to be a promising antifertiliy agants devoids of side effects.
- Antidiebetic effects;- a randomized, placebo-controlled cross-over single blind trial on 40 human voluntiers suffering from type II diebeties was performed. During the four week trial,subjects alernatively received a daily dose of 2.5 gm of tulsi leaves powder or a placebo for two week periods. The results showed 17.6 % decline in post parandial blood glucose on treatment with tulsi as compaired to the blood glucose levels during treatment with placebo[23].
- For heart ailments;- as ‘tulsi’(basil) has a positive effect over blood pressure and also a de-toxicant,its regular use prevents heartattack. A tonic ,may be prepared by mixing one gm of dry tulsi leaves with a spoon full of butter and some candysugar or honey. Take twice a day, first in the morning and before going to bed at night. The drinking of tulsi-leaf tea keeps the blood pressure even.
- Other effects;- the leaves in the form of a paste are used in parasitical diseases ofn the skin and also applied to the figure and toe nails during fever when the limbs are cold. The juice of leaves is given in catarrh and bronchitis in children. The plant is said to have carminative ,diphoratic and stimulant properties. A decoction of the plant is used for cough and also as mouth wash for relieving tooth ache. It is good for head ache,convulsions,cramps,fevers and cholera. The drinking of tulsi tea keeps one free from cough and cold and other ailiments associated with’kapha’dosha in the body. This tulsi tea is an instant pick-me-up(energy drink)[24].

Marketed Products;Stream X Detox(Capsules),Tilasi Arka,Panch Tulsi,Pancha Tulasi(As Lozenge) Etc.

4.Angelica Species;- Traditionally,angelica sinensis,because of its high phytosterogenic content, is reputed to have a stabilizing effects on the female hormonal system , making it usefull in treating menstrual problems. In china, it is often reffered to as ‘female ginseng’. It is also one of the more commonly prescribed herbs , used to nourish blood. Its roots and leaves are commonly used for its medicinal purpose. Constituents of A.sinensis include ligustilide,butyliene pthalide and sitosterol[25].

Essential oil extract from angelica were shown to inhibit selective pathogen and polysaccharides were shown to induce activation of both specific and non specific immune components[26]. One study tested 8 constituents of angelica dahurica root for antifungal and antibacterial activity. 5,8-di (2,3-dihydroxy-3-methylbutoxy)-psoralen was found to be highly toxic to aspergillus candidus. These aeromatic compound intercalates between DNAs,cross links bases when exposed to light, and produces genotoxic effects. Apart from its effects on fungi ,

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

psoralen was later shown to cause cell cycle delays in saccharomyces cerevisiae, and had a bactericidal effects on S.aureus,and E.coli as well[27]. Ferullic acid and byakangelicin from A.dahurica inhibited cladosporiumherbarum growth while (R) – heraclanol showed potent antibacterial activity against bacillus subtilis[28]. These furocumarins induce toxicity,mainly by causing abnormal DNAs – protein interactions or DNA inter-strands interactions[29]. The resistance of some microbes to these furocumarin may be due to the presence of feruloyl catabolising enzymes in the later study, a polysaccharides ,angelin,isolated from the roots of angelica gigas,was shown to trigger the release of cytokinins IL-2,-4,-6 and INF-from macrophages[30].

Cytokine – release was found to occure in a sequential manner,with IL-6 presnting an almost immediate increase ,followed by IL-4,with IL-2,having the slowest rate of increase[31].

The increase of IL-2 may attributed to the preceding increase in the IL-6. In accord with the type of cytokine released it can be postulated that with the initial rapid rise in mediators that activated TH2 cells,the primary effect of angelan is the enhancement of the Tcell-dependent antibody production.

5.Astragalus membranaceus;- native to northern china , shen nang regarded astragalus membranaceus as one of the most important herbs containg active constituents such as glucuronic acid sitosterol,astrgalosides,isoflavon and aspargines[32]. It is usually taken to manage condition of fatigue , loss of appetite and diarrhea.

Atragalus has also been traditionally used to streangthen the immune system and as treatment for respiratory infections..IL-6 mRNA expression was found to be suppressedl[33].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

Fig 5.1

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

Fig.5.2

Have shown that water –soluble extracts of aspargalus radix were able to stimulate the proliferation of splenic lymphocytes,as well as increase the mRNA expression of the cytokine (IL-1,IL-6 and TNF). The extract also increased IL-1 and IL-2 as well as macrophage activity in the immunosuppresed mouse.

The latter finding is in accord with earlier studies of wang et al. that astragali pollsaccharides increased macrophage count,1426 current medicinal chemistry,2004 volume 11 ,number 11 10 and vanitha and promoted opsonization,via the C3 complement component[34].

Ganoderma lucidum;- the virtues of ganoderma have resulted in the documentation of this herbal fungus as one of the superior grade herbs, and as having the most effective healing powers, in some instances,even exceeding the reputation of ginseng. The antiaging effect of these medicinal fungus have also been clearly demonstrated. Its traditionally accepted benefits include removal of toxins, healing of stomach diseases and combarting mushroom poisoning also known as the 'king of herbs', ganoderma was among those herbs that were used to streanghthen the immune system[35].

A glycoprotiene from the water-soluble fractions of the crude extracts was found to activate IL-1.IL-2 and IFN. Fucose residue on this glycoprotein were foumd to be indispensible for these activity. Polysaccharides from

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

fruiting bodies were also shown to increase lavels of IL-1,IL-6,IFN and TNF. Specifically,3 pollysaccharides isolates were able to stimulate activation and proliferation of B and T cells. All three glucans possess D-glucopyranosyl residues. Earlier studies performed on spore of G.lucidum had confirmed that glucans with glucopyranosyl residues had immune stimulating properties[36] another proteoglycan isolated from fruiting bodies,termed GLIS,specifically induces Bcells to express activation and proliferation markers on the cell membranes .

Constiquently,increase in plasma Bcell count and circulating antibodies were noted the finding parallels the reported increases in TH2 and B cell-activating cytokines,IL-1 and IL-6[37]. Both water soluble and ethanol soluble extracts from fruiting bodies were also shown to increase natural killer cell count[38],validating earlier reports of enhance IFN production by polysaccharide derivates. IFN may also be responsible for the increase in differentiation and activationof dendritic cells(DC). Zi and Li reported that APCs,particularly DCs,were found to be stimulated in the presence of polysaccharides. DC,which are major antigen processor, present the processed antigen to Tcells, which in turn areactivated.

Hence,an indirect activation of Tcells may be achieved through increased activation of DC[39]. The increased activation of Tcells reported by sahar et al. may , theirfore be attributed to stimulation of Dc.

Marketed Products;Immune Renew,Now Astragalous,Optimal Immune Extract Power Etc.

6.Ginseng Species;- ginseng is one of the most popular herbs in the world. The medical benefits of ginseng have

Fig 6.1

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

Their roots in Chinese folklore. An anecdotal report of a farmers discovery thatan injured snake could recover after eating this plant provided the impetus that lead to the discovery of its many fold benefits[40]. The material medica , by shen nung ,records ginseng as one of the highest quality herbs. The term 'panax' means 'all healing' in greek. Ginseng has been used for centuries to reduce stress and boost energy containing active ingreadients such as –panax-type ginsenosides,mono and polysaccharides , ginseng is believed to stimulated every aspect of the immune system in the vertebrates. Indeed this is true. Ginsenosides are one of the major constituents of ginseng,with over 28 types identified so far. These steroidal sponins were shown to enhance both B and T cells- mediated immune responses[41] many constituents of ginseng stimulate the immnune system;

Protopanaxadiaol and protopanaxatriol induce proliferation of lymphocytes and cytokines;

Fig 6.2

Rhamnogalacturonan II ginsenosides stimulates IL-6 activity and ginsan (an acidic polysaccharide) induces activities of IL-1,IL-12,TNF and IFN[43]. Several of these constituents have been deemed responsible for the antimicrobial property of ginseng. Acidic polsachharides isolated from panax ginseng have been shown to inhibit helicobacter pylori induced heamaglutination ,possibly due to the presence of uronic acids,a major component of the acidic polysaccharide[44]. Another polysaccharide isolated from P.ginseng also decreased concentration of S.aureus in the plasma in a dose dependent manner this effect may in part be due to the increased acvtivition of macrophages[45] as well as interamacrophage level of nitric oxide, leading to significant bacterial cytotoxicity. Proteins have recently been found in ginseng penanotin, from the roots of panax notoginseng was found to be toxic to coprinus comatus,physalospora pircola and the phytopathogens, botrytis cineria and fusarium oxysporum[46]. Other proteins isolated from the panax family(panaxagin and quinqueginsin) also exhibit antifungal activity panaxging seems to have some conserved residues in its N-terminal sequence wich have been deemed important for fungal ribosome inactivation. Hence ,it has been postulated that panaxaging may exert its antifungal activity as a ribosome inactivating protein[47].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

Marketed Products;Panax Ginseng Capsules,Asian White Ginseng,Naturyz Tripple Ginseng Etc.

7.Gingiber Officinale:-ginger is indigenous to southeast asia;a city with its Sanskrit name ,shunti,was already in existence in 200 B.C.In ayruvedic medicine , ginger is called "The Great Medicament" and is generally used to treat a variety of ailments.This holds true in Chinese culture too.Shen Nung was one of the first to mention dried ginger as a medicament.Known to be a classic gastric tonic, this tropical rhizome is recommended for gastric pain, vomiting,diarrhea,cough and cold.Little wonder then that Chinese sailors chewed ginger to prevent and treat seasickness.It contains more than 20 active compounds,including curcumene and gingerol derivatives.ginger is a domestic remedy also known for its antiinfectant effects.Essential oil constituents from rhizomes of Z.Officinale were found to decrease growth rate of a variety of bacteria and fungi,including

Fig.7.1

Staphlococcus and Candida.The most effective antimicrobial constituent was found to be citral.Curcumene,a sesquiterpene,from ginger oil was found to inhibit Rhizoctonia solani[48].In another advance,it was shown that ethanol extract of Z.officinale were able to inhibit growth of both gram-negative and gram-positive bacteria,although the inhibitory effect was more pronounced for gram-positive bacteria[49].Bactericidal activity against the highly resistant gram-negative bacteria Pseudomonas aeruginosa was notable[50].One of the constituents described for its antifungal activity is dehydrozingeron.Another structurally characterized

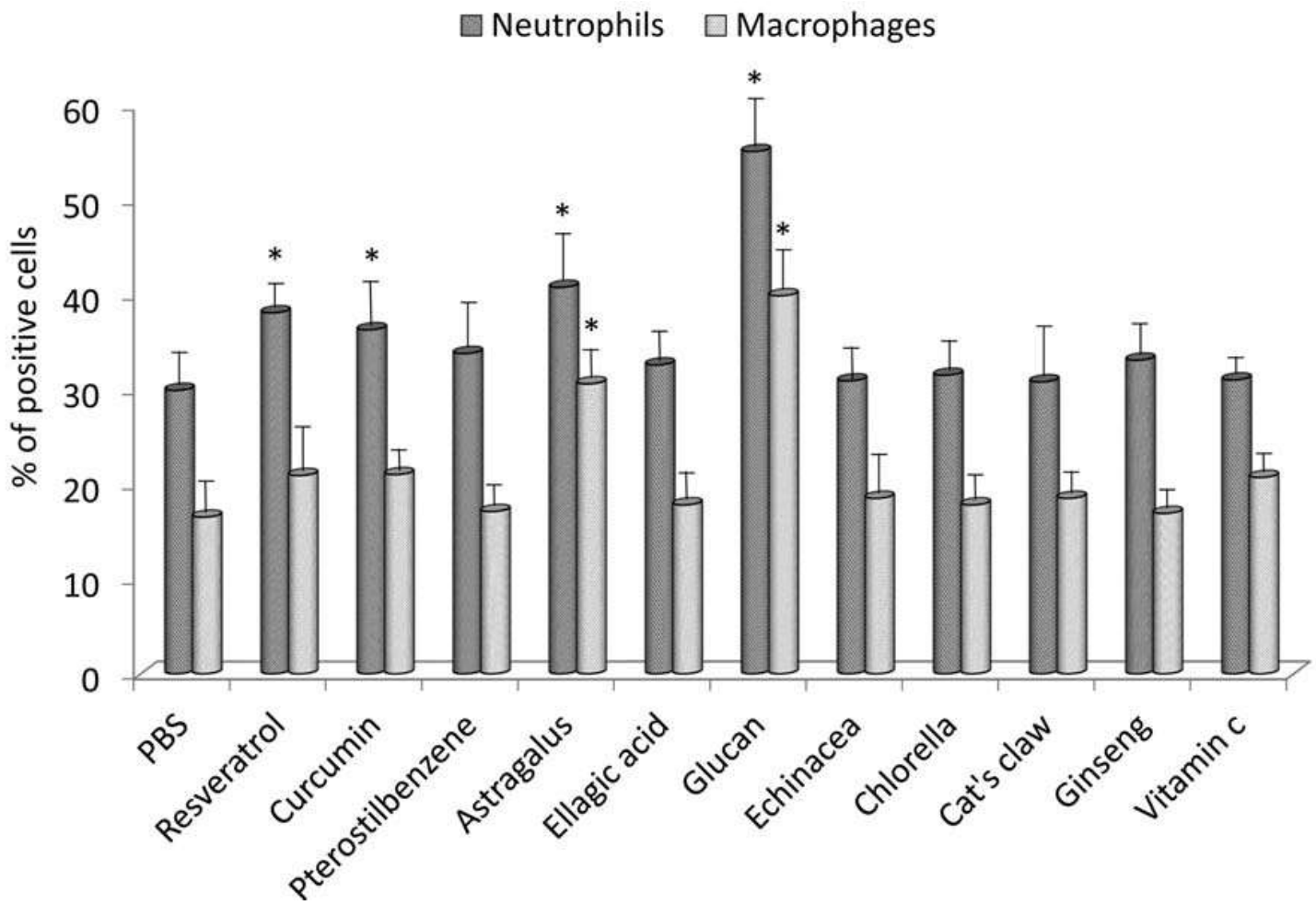
ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

compound,1,7-bis(4-hydroxy-3-methoxyphenyl)hept-4-en-3-one also showed inhibitory effects on Pyricularia oryzae[51].This structure seems to be the skeletal structure of a shogasulfonic acid isolated by Yumiko et al[52].Ethanol-soluble extracts from the rhizome of Z.officinale were tested for their action on cytokines and found to promote the secretion of IL-1 and IL-6 in a time and dose-dependent manner[53].Early isolation experiments showed the presence of highly cytotoxic compounds (diacetylafzelin,diferuloylmethane,feruloyl-p-coumaroylmethaneanddi-pcoumaroylmethane)from the species of the family Gingiberaceae. Pure Gingiberis isolates have been structurally characterized,but their anti-microbial effects were not studied.

Marketed Products; Biopro Liver Support+Detox,Herbal Secrets Turmeric Curcumin,Etc.

Graphical Representation Of Increase In %Of Increase In Positive Cells By Use Of Herbal Immunomodulators



ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

7.Herbal Toxicology

In contrast to chemically synthesized medicinal drugs,herbs are generally thought to be harmless.However,herbal poisoning is not as uncommom as previously thought because of numerous herb-drug intractions,and high concentrations of metabolites that are toxic,when taken improperly.For example,selenium(se)toxicity[55], associated with high concentrations of Se is believed to be due to the continuous generation of free radicals,such as superoxide and their derivatives.Astragalus is an example of a plant that is able to grow in selenium rich areas ,and is able to store large amount of Se.At extremely high concentration,its metabolites ,hydrogen selenide,is formed,which appears to be a major factor causing hepatotoxicity. Animal toxicity studies determined that while L-seleno derivatives were not toxic to animals at low doses,high concentrations of either isomers were noxious[56].

Pyrrolizidine alkaloids(PA) are highly toxic compounds found mostly in the leaves of plants such as Heliotropium spp. And Crotolaria sp..Roder provides explicit information on the presence of these alkaloids in Chinese medicinal plants,while Denham evaluated their hepatotoxicity[57]. More recently ,Deng has highlighted the hepatotoxicity of other herbs like jin Bu Huan (Lycopocium serratum).The herbs reviewed here,however,have not been shown to be hepatotoxic when taken according to prescription.They are also not known to contain significant amount of Pas[58].

Adriane and Ikegami have written two informative reviews on the effects of herb-drug intractions.It should be noted that these intractions do occur ,and are a major cause of health complications in herb consumers.In this regard,pharmaco-vigilance is of critical importance to minimize or avoid the occurrence of such deleterious effects.As a safeguard,it is also crucial that the consumer , especially if he is taking western drugs have access to information on potential herb drug interactions from reliable sources before starting on herbs[59].

In summary , a review of the existing literature has illuminated the existence of specific chemical entities in seven TCM herbs with immunomodulating and antimicrobial activities .i is however not possible to conclude with any great certainty that these compounds are solely responsible for a particular herb's effects as several of these herbs are given in combination in TCM formulae. It appears that they act in concert to produce the desire outcome. It also seem possible that as yet undiscovered compounds from such herbs may exert differing and possibly synergistic effects on host immunity as well as against microbes. The identification and evaluation of new bioactive compounds from herbs can help in the development of noval drugs, leading the way to discovering interesting,possibly less harmfull,and also clinically usefull combinations , to support the immune system as well as inhibit or kill microbes[60]

7.1 Multi-Ingredient Herbal Mixture;

IN many cases, the effects of a single herb result from the overall activities of its constituents. For example,as shown in the case of A.mebrananceus , the general increase in B cells is due to the balance effects between the decreases in IL-6 and IFM. Various factors influence the concentration of bioactive compounds in the herbs.the proportion of constituents may vary in different parts of the plant and age of the plant , the timing of its harvest and soil conditions can all affect the efficacy of the constituents. For example, where ginseng is concered, it is

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

generally believed that the older the root , the greater the concentration of ginsenoside and the more potent its activity. The relative labels of each cytokine may finally be affected by the presence of other herbs as well[73].

Although their have been relatively few reports validating the benefits of herb combination, research into this area is increasing. Investication into the effects of herbal formulas would prove to be rather usefull since multiingredients priscription are a norm in Chinese medicines. The need totaste the effects of prescribed formulas is prudent as the activity of a particular herb in a ,mixture might differ from its activity as a single entity.

"Xiao_Chaia Hu Tang"(XCHT) is a seven-herb mixture that include scutellaria baicalensis, panax ginseng and gigiber officinale. Experiments have shown that XCHT is able to act as a free radical scavenging herbal product and is specially usefull in preventing CC14-induced liver damage. Its antioxidant activity is largly attributed to a major constituent in the mixture , bupleurum,from S.baicalensis. however, reports have shown that S.baicalensis is also able to exert antioxidant activities primarly by increasing production of Hydrogen per oxide. In another example, the 10- ingreadient mixture"Bu Zhong Yi Qi Tang" (which include extragalas membranaceous, panax ginseng, angelica sinensis and gingiber officinale) inhibited proliferation of hepatoma cells more significantly,compared to the inhibitory effects of individual herbs. Hence the different mechanism of action of the herbs in the combination appear to synergise to achieve optimal effects[74].

8. Discussion and conclusion :

The six medicinal herbs reviewed here are commonly used in many prescriptions of local TCM practitioners. In addition to their easy availability,the many benefits of these herbs are also internationally recognized[61]. In TCM practice prescriptions are made for various combinations of the herbs, is in different amounts. For this reson, it is not possible to conclude whether a single herb from a prescription or a single compound from a particular herb , is sollaly responsible for the effect on the immune system[62]

Nonetheless, it is usefull to recognize the molecular and biochemical effects of constituents, isolated from individual herbs, as they may explain the basis for the purported immunomodulatorty and antimicrobial effects of the herbs. This review shows that herbs exert immunostimulating effects in the many ways. Immunostimmulatory agaents do not directly affects immnune memory cell[63], as activation and differerntiation of memory cells require presice cell and MHC-antigen interaction[64]. However, they are specific in that immunostimulants enhance particular immune responses to combart specific pathogens[65]. immunostimulating activities matbe divided into those that (1).enhance phagocytic activities and (2).effect cell –mediated and humoral immunuity.constituents that stimulates phagocytic activities include ginsan (polysaccharide from ginseng) and astragali radix extracts. In this review, it was found that virtually all the herbs have stimulatory effects on humoral immunity[66].

Herbs constituents such as aloeride (polysaccharide from aloe vera),angelan (polysaccharide from angelica gigas)[67], glucopyranosyl- containing polysaccharides(from ganoderma lucidum), ginsenosides(from ginseng) and gingerols (from gigiber officinale)[68] induce the activity of IL-6, a potent Bcell stimulant. As many specific

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

immune responses require T helper cells, it is not unexpected to find many of these constituents being able to stimulate cell mediated immunity as well[69].

The extracts were also shown to selectively stimulate cytokine release , confirming that specific herbs are used to combart bacteria , fungi and viral induced infections. In most cases , polysachharides proteoglycans and flavonoids play a major role in preventing or controlling infectious microbes. Some of these constituents directly disable the pathogens, by disengaging their virulence factors, as well as inhibiting their growth rates. Furocumarins from angelica[70] species present a hazard to microbes, possibly by inducing genotoxic effects. Ithas been hypothesized that penexagene from ginseng works as a fungal ribosome inactivating protein , thus exerting its antifungal effects[71]. Some ginsenosides may be able to interact with phospholipid derivatives on the cell membrane of microbes, causing toxitcity by deestabilishing cell structure. These effects may also prevent microbial attachment to host cells . such actions can limit the damage done to the host by pathogenic bacteria. Thus , in addition to enhancing the immnune response, the antimicrobial effects of these herbs are beneficial to the host[72].

9. References

1.Benjamini,E.;Coico,R.;Sunshine,G.Immunology;a short course (4th edition),Wiley-Liss:Canada,US,2000.

2.J.David Phillipson.Phytochem.**2001**,56(3):237-243.

3.Farnswort,N.R **1990**.The role of ethnopharmacology in drug development,P. 2-11.In:D.J.Chadwick and J.Marsh(eds.).Bioactive compound from plants.Ciba Foundation Symposium 154.Wiley, UK.

4.Canadian Pharmaceutical Association(CPA).**1988**.Self medication.1785Alta Vista Drive ,Ottawa,Canada.

5.Dixon,R.A;Dey,P.M;Lamb,C.J.Adv enzyme.**1983**,55,1-69.

6.Levin, D.A;York,B.M.Biochem Syst and Ecol.**1978**,6,61-76.

7.George,J;Bais, H.P;, Ravishankar,G.A. Critical Rev in Biotech.**2000**,20(1),49-77.

8. Nosten,F;White,N.J.Medecine et Maladies Infectieuses.**1999**,29(3),307-315.

9.Chen,P.,Lu,Y.B.,Lin,C.C.Concepts and theories of traditional Chinese Medicines.Advanced TCM Series Volume 2;Science Press,Beijing,**1997**.

10.Henry C,Lu.Legendary Chinese healing herbs.Sterling Publishing Co.,Inc.New York,USA,**1991**.

11.Wong.K.C;Wu,L.T.The History of Chinese Medicine;2nd edition;National Quarantine Service:Shanghai CH,PP 1-97.

12.Bensky,D.; Gamble ,A. Chinese herbal medicine ;Materica Medica (revised edition) Eastland Press Inc, Seattle,USA,**1993.**

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

13.Pugh,N.; Ross, S.A.; EISohly,M.A.; Pasco, D.S. J. Agric. Food Chem.**2001**,1030-1034

14.Crewe J.E. Minnesota Medicine.**1939**,22,538-539.

15.Lorenzetti,L.J; Salisbury, R; Beal,J.L.; Baldwin, J.N. J. Pharm Sci. **1964**, 53, 1287.

16. Stuart, R.W.; Lefkowitz,S.S. Int J Immunopharm **1997**, 19 (2),75-82.

17.Grinday,D.; Reynolds, T.J. Ethnopharm **1986**,117-151.

18.Egger,S.F.; Brown, G.S.; Kelsey ,L.S.; Yates,K.M.; Rosenberg,L.J.; Talmadge, J.E. Int J Immunopharm .**1996**,18(2) 113-126.

19. Zhang ,L.; Tizard, I.R. Immunopharm.**1996**,35,119-128.

20. Jae, K.L.; Myung K.L.; Yeo, P.Y.; Young, S.K.; Jong, S.K.; Yeong,S.K.; Kyung, J.K.; S.H.; Chong ,Int Immunopharm.**2001**, 1(7),1275-1284.

21. Womble D.; Helderman,J.H. Immunopharm and immnotoxic. **1992**,14, 63-77.

22. Elgayyar, M.; Draughon, F.A.; Golden,D.A.; Mount, J.R. J. Food Prot.**2001**, 64 (7), 1019-1024.

23. Ahn,K.S.; Woong,S.S.; Hwan, M.K.;Sang,B.H.; Kim, I.H. Biotech letters.**1998**,20(1),5-7.

24. Kwon, Y.S.; Kobayashi,A.; Kajiyama,S.I.; Kawazu,K.; Kanzaki,H.; Kim, C.M. Phytochem.**1997**,44(5),887-889.

25. L1ano ,J.; Raber ,J.; Eriksson,L.A. J. Photochem and Photobio A: Chem. **2003**, 154(2-3),235-243.

26. Grossmann,K.F.; Ward, A.M.; Matkovic,M.E.; Folias, A.E.; Moses, R.E. Mutation Research\DNA Repair.**2001**, 487(3-4), 73-83

27. Bintsis, T.; Litopoulou-Tzanetaki, E.; Davies, R.; Robinson, R.K. Food Microb.**2000**, 17(6),687-695.

28. Bordin,F.Int J Photoenergy.**1999**,(1).

29. Ronald P.de vries, Jaap Visser.Microbiol and mole Biol Rev . **2001**,65(4),497-522.

30.Sanf,B.H.;Young,H.K.;Chang,WL;Sum,MP;Hae,Y.L.;Kyung,S.A.;IK,H.K.;Hwan,MK;Immunopharm **1998**,40 (1),39-48.

31. Song, Q.H.; Kobayashi, T.; Xiu, L.M.; Tie,H.; Cyong,J.C. J. Ethnopharm.**2000**, 73 (1-2), 111-119.

32. Young, S.L.; Ok,K.H.; Chan, W.P.; Seong, I.S.; Sang,W.S.; Chae, H.Y.; Tae, W.J.; Eun, S.L.; Kwang J.K.; Seong, H.K.; Wang, K.Y.; Hyo, J.K. Ethnopharm.**2003**,84, 193-198.

33. Wang, J.; Ito,H.; Shimura,K. Jap J Pharm. **1989**, 5, 432-434.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

34. Xiao,P.G.; Xing, S.T.; Wang,L.W. J Ethnopharm. **1993**, 38(2-3), 159-165.

35. Wang,Y.Y.; Khoo,K.H.; Chen, S.T.; Lin,C.C.; Wong,C.H.; Lin, C.H. Bioorg and Med Chem.**2002**, 10(4), 1057-1062.

36. Wang,S.Y.; Hsu,M.L.; Hsu, H.C.; Tzeng,C.H.; Lee,S.S.; Siao, M.S.; Ho, C.K. Int J Cancer.**1997**, 70, 699-705.

37. Bao,X.F.; Wang,X.S.; Qun, D.; Fang,J.N.; Li, X.Y. Phytochem.**2002**, 59(2),175-181.

38. Bao, X.F.; Liu, C.P.; Fang, Li,X.Y. Carbo Res. **2001**, 332,67-74.

39. Zhang, J.S.; Tang, Martin,Z.K.; Reutter, W.; Fan, H. Life Science.**2002**, 71 (6),623-638.

40. Ha,C.L. Nutri Res. **2003**,23(5),691-701

41. Li, Z.C.; Zhi, B.L. Immuno Letters. **2002**, 83(3),163-169.

42. Sahar,E.M.;Meselhy,R.M.; Nakamura,N.; Tezuka, Y.; Hattori, M.; Kakiuchi,N.; Shimotohno, K.; Kawahata,T.; Otake,T. Phytochem.**1998**, 49(6),1651-1657.

43. Reid,D.P. Chinese herbal medicine. Shambhala: Boston,USA,**1987**.

44. Shibata,S.J. Korean Med.Sci.**2001**, 28-37.

45. Kim, J.Y.; Germolec, D.R.; Luster, M.I. Immunotoxicol,**1990**, 12(2), 257-76.

46. Jae, Y.C.; Ae, R.K.; Eun, S.Y.; Kyoung, U.B.; Myung, H.P. Planta Med. **2002**, 497-500.

47. Kwang, S.S.; Kiyohara, H.; Matsumoto, Yamada,H. Carbo Res. **1998**, 307, 97-106.

48. Song, J.Y.; Han,S.K.; Son,E.H.; Pyo, S.N.; Yun, Y.S.; Yi, S.Y. Int Immunopharm. **2002**, 2(7),857-865.

49. Belogortseva,N.I.; Ji Y.Y.; Kyung H.K. Planta Med.**2000**, 3, 217-220.

50. Lim,D.S.; Bae,K.G.; Jung,I.S.; Kim,C.H.; Yun,Y.S.; Song,J.Y. J. Infect **2002**, 45, 32-38.

51. Kwang,S.S.; Kiyohara, H.; Matsumoto, T.; Yamada,H. Carbo Res. **1997**, 300, 239-249.

52. Lam,S.K.; Ng, T.B. Planta Med. **2002**, 11, 1024-1028.

53. Tzi,B.N.; Wang, H. Life Sciences.**2001**,68, 739-749.

54. Isis M. Van Loon,N.D. Alt Med Rev. **1997**, 2(6),472-480.

55. Sato, Y.; Suzaki,S.; Nishikawa, T.; Kihara, M.; Shibata, H.; Higuti,T.J. Ethnopharm. **2000**, 72, 483-488.

56. Masahiro; K.; Inagaki; Nagai; Hiroichi. Planta Med. **2000**,1, 20-25.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

57. Chang,H.M, But. Pharmacology and applications of Chinese Materica Medica, **1986**; Vol 1. Scientific ,Singapore, pp 1022.

58. Huang K.C.The Pharmacology Of Chinese Herbs. CRC Press, Boca Raton, **1993**; pp 291.

59. Franzblav,S.G.; Cross, C.J. Ethnopharm. **1986**, 15, 279-288.

60. Hyung,M.K.;Eun,J.M.; En. L.; Kun, M.K.; Sang, Y.N.; Cha, K.V. Toxicol.**1999**, 135, 109-115.

61. Jen H.C.; Ing, S.L.; Ming, Y.S.; Hsiu, L.C.; Ai, C.C.; Wing,Y.L.; Chew,W.W. Planta Med. **2002**,68, 1036-1039.

62. Skalta , H.D.; Lazari, D.M.; Mavromati, A.S.; Tiligada, E.A.; Constantinidis,T.A. Planta Med. **2000**, 66 , 672-674.

63. Cole, M.D.; Bridge,P.D.;Joanne, E.D.; Fellows, L.E.; Cornish, M.C.; Anderson,J.C. Phytochem. **1991**, 30 (4), 1125-1127.

64. Martins, A.P.' Salguelro,L.; Goncalves, M.J.; Proenca da Cunha, A.; Vila, R.; Cafigueral, S.; Mazzoni, V.; Tomi, F.; Casanova, J. Planta Med.**2001**, 67,580-584.

65. Agarwal,M. Pest Manag Sci.2001, 57(3),289-300.

66. Mascol,N.; Jainb,R.; Jaw,S.C; Capasso, F.J. Ethnopharm. **1989**, 27, 129-140.

67. Alzorekya, N.S.; Nakahara, K. Int J Food Microbiol.**2003**, 80, 223-230.

68. Habsah, M.; Amran, M.; Mackeen, M M.; Lajis, N.H.; Kikuzaki, H.; Nakatani, N.; Rahman, A.A.; Ghafar; Ali, A. M. J . Ethnopharm. **2000**, 72, 403-410.

69. Ramos Ruiz, A.; De la Torre, R.A.; Alonso, N.; Villaescusa, A.; Betancourt , J.; Vizoso, A.J. Ethnopharm. **1996**, 52, 123-127.

70. Endo, K.; Kanno, E.; Oshima, Y. Phytochem. **1990**, 29, 797-799.

71. Hori, Y.; Miura, T.;Hirai, Y.; Fukumura, M.; Nemoto, Y.; Toriizuka, K.; Ida., Y. Phytochem.**2003**, 62, 613-617.

72. Chih, P.C.; Jan, Y.C.; Fang, Y.W.; Jan, G.C. J. Ethnopharm. **1995**, 48, 13-19.

73. Matthes,H.W.D.; Lvu,B.; Ourisson, G. Phytochem. **1980**, 19, 2643- 2650.

74. Kwang,S.S.; Kiyohara,H.; Matsumoto,T.; Yamada, H. Carbo Res. **1998**, 307, 97-106.

75. Kwang, S.S.;Kiyohara, H.; Matsumoto, T.; Yamada,H. Carbo Res. **1997**, 300, 239-249.

76. Wong,Y.Y.; Lau,H.S.; Tadi, P.; Teel, R.W. Mut Res. **1992**, 279, 209-216.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

77. Yen, M.H.; Lin, C.C.; Chuang,C.H.; Liu S.Y. J. Ethnopharmacology. **1991**, 34, 155-165.

78. Chou, C.C.; Pan, S.L.; Teng, C.M.; Guh, J.H. Eur J Pharm Sci. **2003**, 19 (5), 403-412.

79. Kao, S.T.; Yeh, C.C.; Hsieh, C.C.; Yang,M.D.; Lee, M.R.; Liu, H.S.; Lin, J.G.Life Sci. **2001**, 69, 1485-1496.

80. Spallholz,J.E.; Hoffman, D.J. Aquatic Toxicol.**2002**, 57 (1-2), 27-37.

81. Roder, E. Pharmazie. **2000**,55, 711-726.

82. Denham, A. Eur J Herb Med. **1996**, 2 (3) , 27-38.

83. Deng, J.F. Toxicol.**2002**, 181-182, 571-576.

84. Adriane,F.B.The Lancet. **2000**,355(9198),134-138.

85. Ikegami,F,; Fujii,Y.; Ishihara, K.; Satoh, T. Chemico-biological Intractions. **2003**, 145(3),235-250.