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RESEARCH ARTICLE

REVIEW:ANTIVIRAL AND IMMUNOMODULATORY PROPERTIES OF NUTRACEUTICALS AND HERBS

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Abstract

The antiviral activities of plant extracts have been renewed and have been the topic of passionatescientific investigation. Several medicinal plant extracts have shown antiviral activities against some RNA and DNA viruses. Therefore, extracts of plants and phytochemicals are getting more importance as potential sources for viral inhibitors during the recent decade. Extensive studies have shown that medicinal plants of several parts of the world contain compounds active against viruses that cause human diseases. Regarding nutraceuticals, many single and combined products have showneffectiveness in enhancing immunity in viral infections including influenza. Depending on the availability; many nutraceuticals can be used to enhance immunity.All the significant findings have been compiled and published in the literature, and the data were analysed critically to provide perspectives and directions for its synergistic use in different combinations or as a single ingredient for the formulation of novel immunomodulating agents. Extensive experimental and preclinical studies on the immunomodulating potential of all herbs and Nutraceuticals should be carried out to provide sufficient data to prove that their traditional uses are inherently effective and safe and will allow clinical trials to be pursued for their further development as therapeutic agents to treat immune-related disorders.

Introduction:-

The contribution of natural products to anti-viral chemotherapy, however, has been more modest. Several factors have contributed to this scenario. Viral infections like the common cold are self-limited and require only symptomatic treatment. A large number of plants found in India have, therefore been investigated and found active in Japan, South Korea, US, etc. Plants active in viruses closely related to human virus [e.g. feline Human Immunodeficiency Virus (HIV) or duck hepatitis] have also been included[1].Several hundred plant and herb species that have potentialas novel antiviral agents have been studied, with surprisinglylittle overlap. A wide variety of active phytochemicals,including the flavonoids, terpenoids, lignans,sulphides, polyphenolics, coumarins, saponins, furylcompounds,alkaloids, polyines, thiophenes, proteins andpeptides have been identified. Some volatile essential oilsof commonly used culinary herbs, spices and herbal teashave also exhibited a high level of antiviral activity.[2]

Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the

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viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host‐ specific interactions. In this brief report, we summarize the antiviral activities from several natural products and herbal medicines against some notable viral pathogens including coronavirus (CoV), coxsackievirus (CV), dengue virus (DENV), enterovirus 71 (EV71), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, human immunodeficiency virus (HIV), influenza virus, measles virus (MV), and respiratory syncytial virus (RSV).[3]

About one-quarter of marketed orthodox pharmaceutical medicines is either derived from plantsources or from derivatives of secondary plant metabolites.The success of obtaining new drugs from naturalsources is not very encouraging. Several factors are responsiblefor such observation. Atpresent, of about 2000 varieties of minor illnesses andserious diseases only 40% have cure using conventionalorthodox pharmaceuticals. Variouschemicals and biotechnological products are beingscreened by major multinational pharmaceutical industriesin the hope of discovering new cures for diseases. [4]

Complementary and alternative medicine offers a wide variety of herbal plants, which may serve as key to unlock the many mysteries behind human pathologies. According to a World Health Organization (WHO) report, 80 % of the population in developing countries depends on traditional plants for health requirements. [5]Natural products such as herbal plant extracts (used in Ayurveda as mentionedinCharaka Samhita and Susruta Samhita or other traditional medicine practices), plant derived compounds (also known as phytoconstituents), extracts of specific plant parts (roots, stem, bark, flowers, fruits and seeds), dietary supplements and nutraceuticals find wide application in treating ailments ranging from common to rare infectious and non-infectious diseases.[6],[7]

This review mainly focuses on the effect of herbs and nutraceutical on respiratory health and on viral infections; however, other studies on viral infections have also been included. Finally, practical recommendations have been drawn on both preventive and therapeutic nutritional interventions.

Antiviral and Immunomodulatory Effects of Herbs:

The history of the use of herbs as medication is as old as history itself. Some authors state that the first recorded use of herbs for medical treatment began over 4000 years ago.[8] Theorigin of this type of medical treatment began in China and India. Traditional Chinese medicine centres on interactions between the body and the environment. A mixture of treatments, including herbs, acupuncture, and massage, is then prescribed. Traditional Indian medicine has dated back to 3 000 BC. [9]

***Andrographis paniculate*:**

Andrographis paniculata, commonly known as the "king of bitters," is an herbaceous plant belonging to the Acanthaceae and is found throughout tropical and subtropical Asia, Southeast Asia, and India. In India, A.paniculatais known as "Kalmegh" [10],[11].

Andrographolide is a major bioactive phytoconstituent found in various parts of A. paniculate, but particularly in the leaves.[12]Andrographolide has been reported to significantly reduce the inflammation caused by histamine,dimethyl benzene, and adrenaline.Andrographolide exhibited potent cytotoxic activity against KB (human epidermoid leukaemia) and P388 (lymphocytic leukaemia) cells.[13]A methanol extract was found to inhibitPlasmodium falciparum substantially at a 50% inhibitoryconcentration (IC50) of 7.2 μg/mL.[14]

The ethanolic extractofA. paniculatawas effective against upper respiratory tract infection. [15]A. paniculate has been widely used for upper respiratory tract infections(URTIs). In a randomized, double-blind, and controlledstudy, Thamlikitkul et al.administeredA. paniculataata dose of 6g/day for 7 days to 152 Thai adults suffering frompharyngotonsillitis, and the efficiency has been reported to besimilar to that of acetaminophen in relieving the symptoms offever and sore throat.It had been reported that andrographolide, with oral doses of 100 and 300mg/kg, produced a significant antipyretic effect after 3 h administration of brewer's yeast-induced fever in rats. In addition, doses of 180 or 360mg/kg of andrographolide were also found to relieve fever in humans by the third day after administration. [13]

Andrographolide has been proposed to be a very effective drug against IAV (Influenza A Virus). IAV is a causative agent of respiratory infection in humans, and virus replication takes place in epithelial cells of the upper and lower

respiratory tract. Chen et al. showed that andrographolide and its various derivatives inhibit H9N2, H5N1 and H1N1 strains of influenza virus, both in vitro and in vivo.[16]

Host innate immune factors such as retinoic acid inducible gene-1 (RIG-1)-like receptors (RLRs) are involved in detection of RNA viruses inside the cytoplasm. The RLR family includes RIG-1, MDA5, and LGP2, which, on sensing RNA viruses, induce the initiation and modulation of antiviral immunity of the host.[17] Infection with H1N1 leads to the activation of the RLR dependent signalling pathway. Andrographolide inhibits the H1N1-induced RIG-1-like receptor signalling pathway in human bronchial epithelial cells, indicating inhibition of virus-induced activation of the RLR pathway, leading to amelioration of H1N1-virus-induced cell mortality.[18]Moreover, the effectiveness of A. paniculate extract SHA-10 on patients suffering from the common cold was evaluated by Caceres et al. by visual analogue scale measurement. Their study concluded that SHA-10 dried extract (1200 mg/day) effectively reduced the prevalence and intensity of uncomplicated common cold symptoms at day two of treatment.[19]

The hepatoprotective effects of pre-treatment with various extracts and constituents of A. paniculata are very consistent. [20] Moreover, its inclusion in effective polyherbal formulations for respiratory ailments not amenable to any modern intervention lends support to its potential effectiveness. Existing evidence supports A. paniculata's role in the treatment of Respiratory tract.

***Azadirachtaindica*:**

Azadirachtaindica,commonlycalled'Neem',hasbeenusedintraditionalmedicinesinceantiquity,isregardedas'holytree'.[21],[22]Nimbolide,anactiveneemcomponentfromneemleafsignificantlyinhibitscellviabilitybyinducingapoptosis,andsuppressedcellularinvasionandmigrationthroughabrogatingSTAT3activation.Itsuppressedtumourgrowthandmetastasisintransgenicadenocarcinomaofmouseprostatecancermodel. [23] Neemlimonoidsviz.azadirectinandnimbolidehavebeenreportedtoinducecellcyclearrestandmitochondria-mediatedapoptosisincervicalcancer(HeLa)cellline.[24]

The neem leaf has been reported to exhibit various pharmacological activities, including anti-inflammatory [25], antioxidant [26],[27], antimicrobial [28] and antiviral properties [29]. Neem oil and the bark and leaf extracts have been therapeutically used as folk medicine to control leprosy, intestinal helminthiasis, respiratory disorders, constipation and also as a general health promoter. The plant is reported to have antipyretic, neuropsychological,antimycotic, cardiovascular and immunomodulatory and anti hyperglycemic activity[45]. Active constituents of the neem leaf include nimbin, nimbidine, isomeldenin, β-sitosterol and quercetin [30]. Quercetin [31], β-sitoserol[32] and nimbidine[33]have been shown to exert anti-inflammatory effects. These effects are due to the inhibition of pro-inflammatory molecules, such as TNF-α, iNO S and NF -κB.

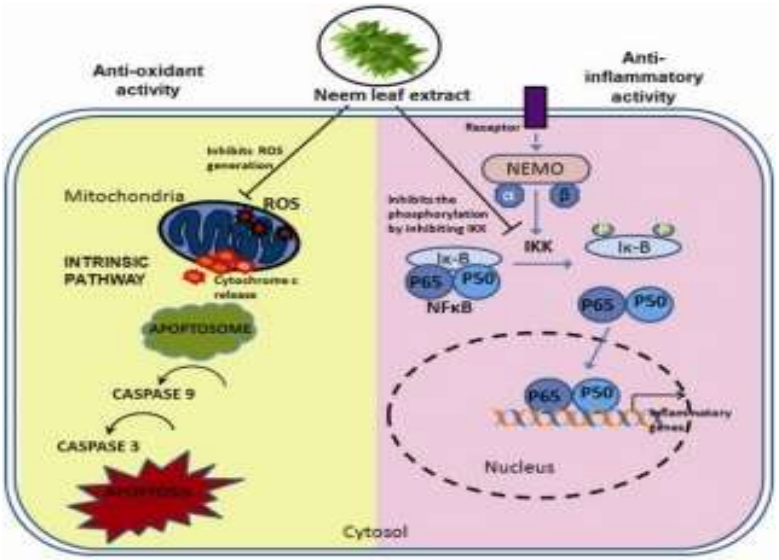

Fig. 1:- Antioxidantandanti-inflammatorymechanismsofneemleafextract.[46].

Neem leafextracts(NLEs)showedanti-oxidant/anti-apoptoticpropertiesbyreducingreactiveoxygenspecies(ROS) generationandinhibitingapoptoticresponsesthroughintrinsic mitochondrialpathway.NLEsalsoshowedanti-inflammatoryresponsesbyinhibitingIkBkinase (IKK)andnuclear translocationofNFκB(nuclearfactorkappaB)fortranscriptionofinflammatorygenes.[46]

In the study conducted by Lee J W et al, it was reported that treatment with NLE (Neem Leaf Extract) significantly attenuated the infiltration of inflammatory cells, such as neutrophils and macrophages in bronchoalveolar lavage fluid (BALF). NLE also reduced the production of reactive oxygen species and the activity of neutrophil elastase in BALF. Moreover, NLE attenuated the release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 in BALF. NLE inhibited the recruitment of inflammatory cells and the expression of monocyte chemoattractant protein-1 (MCP-1) in the lungs of mice with CS- and LPS-induced pulmonary inflammation.[34]

Today, modern societies, finding themselves confounded in the web of their creation, are willing to revert to the nature for remedies and neem tree provides a promising mean in this matter.

***Nigella sativa*:**
Nigella sativa seeds and its oil had been widely used in traditional medicine (particularly in Unani Medicine) for a wide variety of illnesses including bronchial asthma in adults. There are several pharmacologically active constituents in the essential oil of the plant, including thymoquinone (TQ).The adjuvant effect of N.sativaoil in patients of bronchial asthma has already been reported but, no work had yet been done in very common disease of children called wheeze associated lower respiratory tract illness (wheeze associated LRTI).In the study of Ahmed J et al it was found that Nigella sativa seeds has effect in patients of wheeze associated LRTI, particularly in children.[35]

The therapeutic effects of the plant extract against hypertension, asthma, cough, bronchitis, headache, fever, influenzadiabetes and metabolic syndrome complications (e.g. obesity, dyslipidemia, and high blood glucose), cyclic mastalgia (analgesic effects), hand eczema, vitiligo, pediatric seizures, opioid dependence, anxiety, infectious diseases (e.g. infections caused by human immunodeficiency virus, hepatitis C virus, and Helicobacter pylori), infertility, asthma, chemical war injuries, tonsillopharyngitis, allergic rhinitis, rheumatoid arthritis, dyspepsia, celiac disease, and hepatotoxicity of methotrexate were demonstrated in clinical studies .[35],[36],[37],[44]

Other studies used animal models of respiratory disorders to examine the effect of N. sativa extract and its active compounds specially TQ. The preventive effect of hydro-ethanolic extract of N. sativa (0.08 g/kg/day, in drinking water, for 14 days) on tracheal responsiveness and lung inflammation was shown in a guinea pig model of lung injury induced by sulfur mustard.[38],[39]

Gunes et al investigated the effect of TQ treatment (50 mg/kg/day, administered by gavage for 5 days) on lung tissue injury induced by hyperbaric oxygen (HBO_2) therapy, in a rat model. The antioxidant property of TQ led to reduction of lipid hydroperoxide (LOOH) and total sulfhydryl group (-SH) causing a preventive effect on HBO_2 - induced lung injury.[40]In a rabbit model with bacterial rhinosinusitis, N. sativa extract (50, 100, 200 mg/kg/day, administered orally for 7 days) reduced nitric oxide (NO) level and thus, prevented histopathological changes.[41]The study of Kamal E. H et al suggested that VO-induced respiratory effects were mediated via release of histamine withdirect involvement of histaminergic mechanisms and indirect activation of muscarinic cholinergicmechanisms.[42]

The study of Umar S et al determined the possible effects of Nigella sativa on immune-response and pathogenesis of H9N2 avian influenza virus in turkeys.It was found that the higher antibody titre against H9N2 AIV in turkeys fed 6% NS seeds shows the immunomodulatory nature of NS. Similarly, increased cytokine gene expression suggests antiviral behaviour of NS especially in dose dependent manner, leading to suppressed pathogenesis of H9N2 viruses. However, reduced virus shedding and enhanced immune responses were more pronounced in those turkeys received NS.[43]

Nigella sativa seedshave a good antiviral property and is effective against respiratory related illness.

***Phyllantusamarus*:**
The genus Phyllanthus consists of several species in the family Euphorbiaceae. Phyllanthus virgatusand another two species, P. amarusand P. urinaria, are closely related in appearance and phytochemical structure. For example, P. amarusinhibits the growth of human adenocarcinoma cell line Caco-2 [47], hepatoma induced by N - nitrosodiethylamine in rats [48]and sarcoma induced by 20-methylcholanthrene in mice. In Brazil and in many South American countries, the infusion of roots, stems, and leaves of most Phyllanthus species have been used to cure a broad spectrum of diseases including intestinal infections, hepatitis B, diabetes, kidney, and urinary bladder disturbances [49]. In Asia, several Phyllanthus species are used as febrifuge, diuretic, deobstruent, stomachic, and antiseptic. Ayurveda uses the greatest number of Phyllanthus species where 15 species have been used in the management of genitourinary, hypertension, cancer, skin, digestive, hepatic, and respiratory disorders.[50],[51],[52]

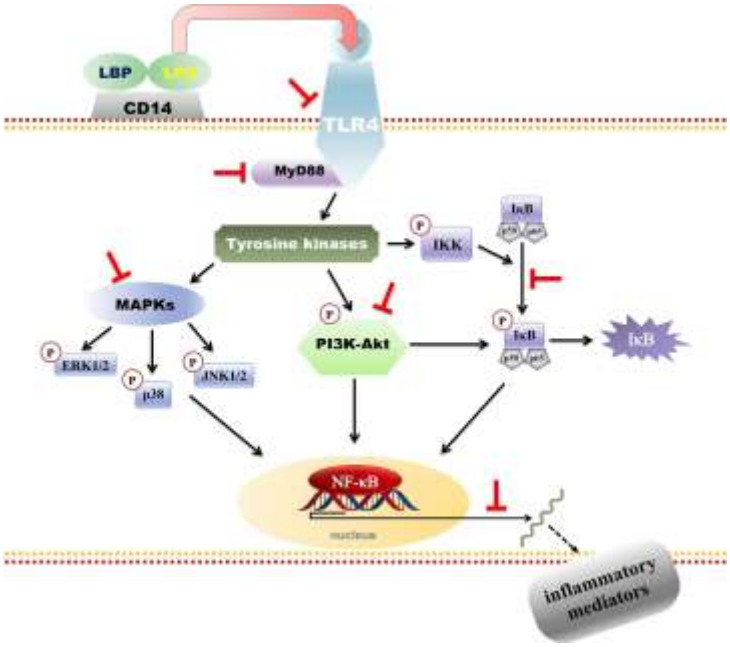

Fig. 2:- Phyllanthin-mediated inhibition of lipopolysaccharide (LPS)-induced inflammatory responses through NF-κB, MAPKs, and PI3K-Akt signalling pathways in human macrophages.[53].

Recently, Harikrishnan et al., (2018a), Harikrishnan et al., (2018b), and Harikrishnan et al., (2018) investigated the effects of 80% ethanol extract of P. amarusand its main constituents, phyllanthin, hypophyllanthin , and niranthin (24–1.5 μM), using LPS-induced U937 human macrophages. They reported that their anti-inflammatory effects were by downregulating the nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3-kinase (PI3K-Akt) signaling pathways. **Fig 2**depicts phyllanthin-mediated inhibition of LPS-induced inflammatory responses through NF-κB, MAPKs, and PI3K-Akt signaling pathways in human macrophages.The results demonstrated that P. amarusextract considerably repressed the aforementioned pro-inflammatory mediators' release and expression of COX-2 protein. Also, the raised mRNA transcription of pro-inflammatory markers was prominently reduced.[54],[55],[56]

A noteworthy inhibition of the percentage of CD4+ and CD8+ expression on spleen cells and in serum cytokines of IL-2 and IFN-γ and IL-4 was seen [57] at a dose of 400 mg/kg of the extract. Interestingly, it was observed that P. amarusadministration raised the levels of cellular GSH and GST, hence reducing the detrimental effects of cyclophosphamide metabolites, a conventional immunosuppressive drug. In subsequent study, standardized P. amarusextract (50–200 mg/kg) effects on cellular and humoral immune responses in mice were investigated [58].Phyllanthin also downregulated anti-sRBC immunoglobulins (IgM and IgG) antibody titer in immunized and phyllanthin-treated mice in a dose-dependent manner with maximum inhibition at 100 mg/kg[59].

Hepatitis B virus claims around a million human lives annually. Sarma and colleagues attempted to explore a potent and efficient antiviral from Phyllanthus with a minimal risk of resistance for hepatitis B virus. Moreover, in this attempt the Phyllanthus active principles from among 93 phytochemicals were isolated to check the mechanism of

action against hepatitis B virus reverse transcriptase (HBV RT), which is an active target for drugs used against HBV infections.[60]

The chemical compounds from Phyllanthus bear diverse biological activities, and providesalternative approach to ongoingtherapy for immunological disorders.

Table 1:- Partial list of viruses inhibited by medicinal plants.

Virus	Medicinal Plant used	Antiviral Effect	Reference
Dengue virus type-2 (DEN-2)	*Azadirachtaindica*Juss. (Neem)	The aqueous extract of neem leaves inhibited DEN-2 both in vitro and in vivo	[61]
Human immunodeficiency virus	*Phyllanthus amarus*Schum. &Thonn.	Inhibits HIV replication both in vitro and in vivo	[62]
Human immunodeficiency virus	*Andrographis paniculata*(Burm.f.) Nees	Antiviral effect through immunomodulation. Increased CD4+ counts and 30% decrease in viral load	[63]
H9N2 avian influenza virus	*Nigella sativa*	Increased cytokine gene expression suggests antiviral behavior of NS, leading to suppressed pathogenesis	[43]
Human immunodeficiency virus	*Tinosporacordifoila*	Protease inhibitors for HIV and drug resistant HIV. Tyramine is a neuro- modulator. Used to treat anxiety and depression by inactivating neurotransmitters	[64],[65]
Chikungunya Virus	*WithaniaSomnifera*	virus clearance in brain and joint tissues on formulation treatment revealed adirect correlation of viral load in brain to morbidity during infection; likewise, joint swelling receded prior to complete viral clearance explaining possibleimmunomodulatory effect	[134]

***Tinosporacordifoila*:**

Tinosporacordifolia[*Tinosporacordifolia*(Willd.) Miers ex Hook. F. &Thoms],known as Gulvelor Guduchi, has been anextensively used and investigated plantfrom family Menispermaceae for its variedactivities. It is a deciduous, fleshy, robustclimber growing with support of mango orneem trees, and is also known as CocculuscordifoliusDec, MenispermumcordifoliumWilld., and Tinospora glabra (N. Brum.)Merr. Giloya, the Hindi name of theplant refers in Hindu mythology to aheavenly elixir used to stay off the agingand to stay young forever. The Sanskritname ―Guduchi means one that protects from illnesses. Hence the words ―rejuvenator or ―adaptogen seem to have appeared in literature.[66]

Tinosporine, Tinosporaside, cordifolide, cordifol, and hepatacosanol are important constituents of Gulvel. Barberine and palmatine are major alkaloids in stem. The glucosides are 18-norclerodane glucoside, sesquiterpenes like tinocordioside, tinocordifolioside, tinocordifolin, tinosponone, and cordioside, cordifolisides, and syringene. The stem contains immunologically active substances –arabinogalactan and (1,4)-alpha-Dglucan[68],[69]. Crude values for food content in Gulvel include high fibre (15.9%), sufficient protein (4.5%-11.2%), sufficient carbohydrate (61.66%), and low fat(3.1%) [70],[71].Nutritive value is 292.54 calories per 100 g[70],[72]. Gulvelhas high potassium (0.845%) (Regulatory function of nerve impulse)[70],[73]high chromium (0.006%) (Regulation of carbohydrate utilization and pathophysiological alternations in diabetes mellitus)[74],[75]sufficient iron (0.28%) (Hematopoietic functions)[70],[76],[77]and sufficient calcium (0.131%) (Regulatory functions in bloodcoagulation, and nervous, cardiovascular, and musculoskeletal systems[70],[78],[79].

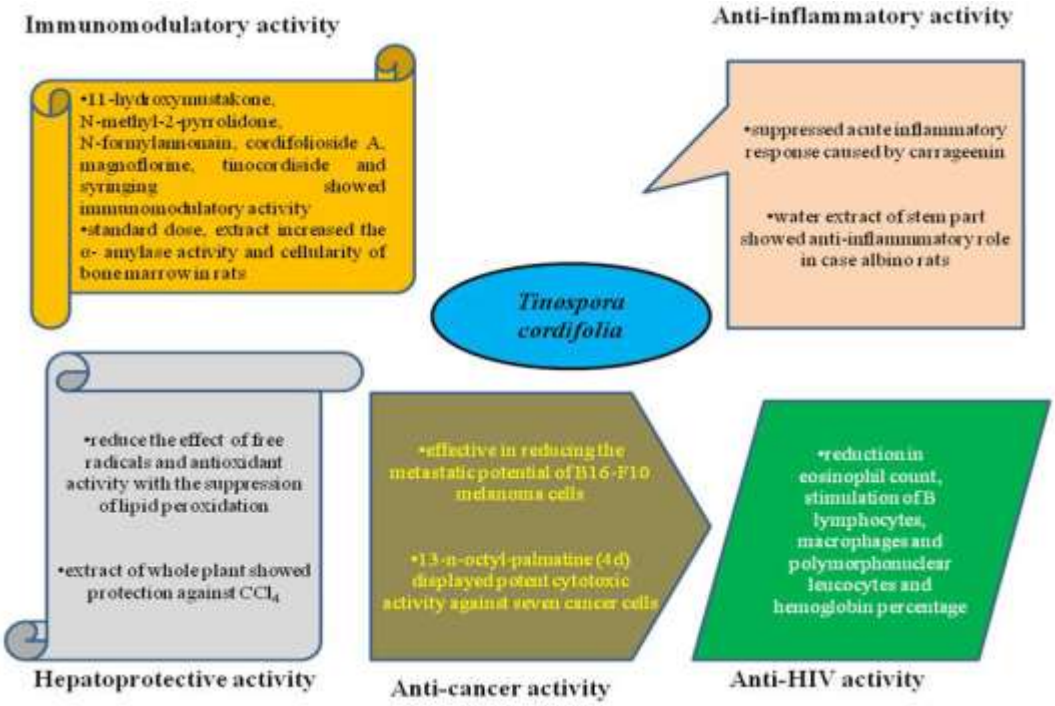

Fig. 3:- Pharmacological property of *Tinosporacordifoila*[80].

It is used in jaundice, cough, piles, fever, respiratory tract infection, intestinal pain, inflammation, gout, rheumatism, leprosy, urinary affections and diarrhea. Pharmacological activity: It is anti-inflammatory, anti-emetic, antiarthritic, anti-diabetic. Sudhakaran et al. reported immunostimulatory effect ofthis plant in Oreochromis mossambicus[81]. Mechanism: *T. cordifolia*exhibits significant immunomodulatory activity by enhancing phagocytic activity ofWBC[82].

The alcoholic extract of T. cordifoliashowed significant immunomodulatory effects. At standard dose, extract increased the α-amylase activity and cellularity of bonemarrow in rats. It had been observed bysome researchers that some activecompounds viz; 11- hydroxymustakone,N- methyl- 2- pyrrolidone, N- formylannonain, cordifoliosideA,magnoflorine, tinocordisideandsyringing showed immunomodulatoryactivity.[83]

The study of Kalikar M et al investigated that theTinosporacordifoliaextract, a plant derived immunostimulant, significantly affected the symptoms of HIV. This was validated by clinical evaluation.Thus, Tinosporacordifoliacould be used as an adjunct to HIV/AIDS management.[84]

The plant possesses anti-oxidant, anti-hyperglycemic, anti-neoplastic, anti-stress, anti-dote, anti-spasmodic, anti-pyretic, antiallergic, anti-leprotic, antiinflammatory, anti hyperlypidaemia, Immunomodulatory properties. Hence, various parts of the plant contain immense medicinal property.[85]

***Withaniasomnifera*:**
Ashwagandha (Withaniasomnifera, fam. Solanaceae) is commonly known as "Indian Winter cherry" or "IndianGinseng". It is one of the most important herbs of Ayurveda (the traditional system of medicine in India) used for millennia as a Rasayana for its wide-ranging health benefits. The biologically active chemical constituents of Withaniasomnifera(WS) include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins. Many of its constituents support immunomodulatory actions.[130],[131].W.somnifera compound, Withanone, docked very well in the binding interface of AEC2-RBD complex, and was found to move slightly towards the interface centre on simulation. Withanone significantly decreased electrostatic component of binding free energies of ACE2-RBD complex. Two salt bridges were also identified at the interface; incorporation of Withanone destabilized these salt bridges and decreased their occupancies.Such an interruption of electrostatic interactions between the RBD and ACE2 would block or weaken COVID-19 entry and its subsequent infectivity.[132]The collaborative study of DAILAB at Indian Institute of Technology (IIT) Delhi and National Institute of Advanced Industrial Science and Technology (AIST), Japan,revealed that the researchers targeted the main SARS-CoV-2 enzyme for splitting proteins, known as the Main protease (Mpro). Mpro plays a key role in mediating viral replication. This is an attractive drug target for this virus, and as humans don't naturally have this enzyme, compounds that target Mpro are likely to have low toxicity. They discovered that a natural compound Withanone (Wi-N) derived from Ashwagandha and Caffeic Acid Phenethyl Ester (CAPE), an active ingredient of New Zealand Propolis, has the potential to interact with and block the activity of Mpro[133].

The Antiviral and Immunomodulatory effects of Vitamins, Trace elements and Nutraceuticals:
Nutraceuticals are dietary supplements, dietary fiber , genetically engineered designer foods, specific diets, and processed foods, such as cereals, soups, and beverages utilized to ameliorate health, delay senescence, prevent diseases, and support proper functioning of human body. Currently nutraceuticals are getting substantial attention due to nutrition and therapeutic potentials. They have benefit over medicine because they avoid side effect. On the basis of their source, they are categories into different terms such as nutrients, dietary supplements, herbals, dietary fibre, etc. Global market for nutraceutical is huge i.e. approximately USD 117 billion. Nutraceuticals are products that claim physiological benefit or protection against chronic disease. [86],[87]

Zinc:
Zinc is an essential trace element which plays an important role in growth, development, and the maintenance of immune function [88],[89]. Zinc deficiency has been associated with an increased susceptibility to infectious diseases, including viral infections. Studies have shown that the zinc status of an individual is a critical factor that can influence immunity against viral infections, with zinc-deficient populations being at increased risk of acquiring infections, such as HIV or HCV [88]. Few RCTs have evaluated the effect of zinc supplementation on the immune response. A study by Acevedo-Murillo et al. among 103 children (1 month to 5 years) with pneumonia showed a statically significant clinical improvement (duration of illness, respiratory rate and oxygen saturation) in the zinc supplemented group compared to placebo [90]. They also demonstrated an increase in the cytokine response in Th1 pattern (IL-2 and INF-γ) only in the zinc group, with Th2 cytokines (IL-4 and IL-10) being elevated or remaining high in both groups. Another RCT on oral supplementation of high-dose zinc (150 mg/day) after stem cell transplantation, demonstrated that it enhances thymic function and the output of new CD4+ naïve T cells, helping to prevent the reactivation of TTV [91]. However, a study by Provincial et al. concluded that although prolonged supplementation with zinc (400 -250 mg/day) or zinc+arginine (4 d/day) in the elderly (age 64-100 years) restores zinc plasma concentrations, it is ineffective in inducing or ameliorating the antibody response or number of CD3, CD4 or CD8 lymphocytes after influenza vaccination[92]

Vitamin C:

Vitamin C is known as an essential antioxidant and enzymatic co-factor for many physiological reactions in the body, such as hormone production, collagen synthesis andimmune potentiation [93]. In-vivo animal studies in mice have shown that it is an essentialfactor for the antiviral immune responses against the influenza A virus (H3N2) through theincreased production of interferon-α/β, especially at the early stages of the infection [93]. However, our literature search was unable to identify RCTs examining the use of vitamin C for the treatment for specific viral infections. Furthermore, a systematic review and meta-analysis on the role of vitamin C for preventing and treating the common cold, did not find any conclusive evidence to indicate that there is benefit of using vitamin C mega dose prophylaxis in the community to reduce the incidence of common cold, which is most often caused by viral infections[94].

Vitamin E:

Vitamin E, a fat-soluble vitamin, is a potent antioxidant and has the ability to modulate host immune functions [95]. Vitamin E deficiency is known to impairs both humoral and cellular immunity [95]. However, few studies have shown that vitamin E supplementation might cause harmful effects on the incidence of infectious disease. A study among 50-69 years old adult smokers showed that vitamin E supplementation increases the risk of pneumonia [96]. Similarly, supplementation of vitamin E (200 IU/day) did not have a statistically significant effect on lower respiratory tract infections in elderly nursing home residents[97]. However positive effects of vitamin E have been observed in the treatment of chronic hepatitis B in a small pilot RCT, where a significantly higher normalization ofliver enzymes and HBV-DNA negativization, was observed in the vitamin E group [98].Similar results have been observed in a RCT in the paediatric population, where vitamin E treatment resulted in a higher anti-HBe seroconversion and virological response [99].

Curcumin:

Curcumin (CUR) plant-derived polyphenol and is the principal curcuminoid of turmeric and possesses strong antioxidant and anti-inflammatory activities[100],[101]. CUR prevented oxidative damage and apoptosis in a rodent model of gentamicin-induced hepato- and nephrotoxicity [100],[101]. Besides its ability to suppress oxidativestress and inflammation, CUR possesses anticancer, anti-atherosclerotic, anti-diabetic and anti-obesityproperties[102].

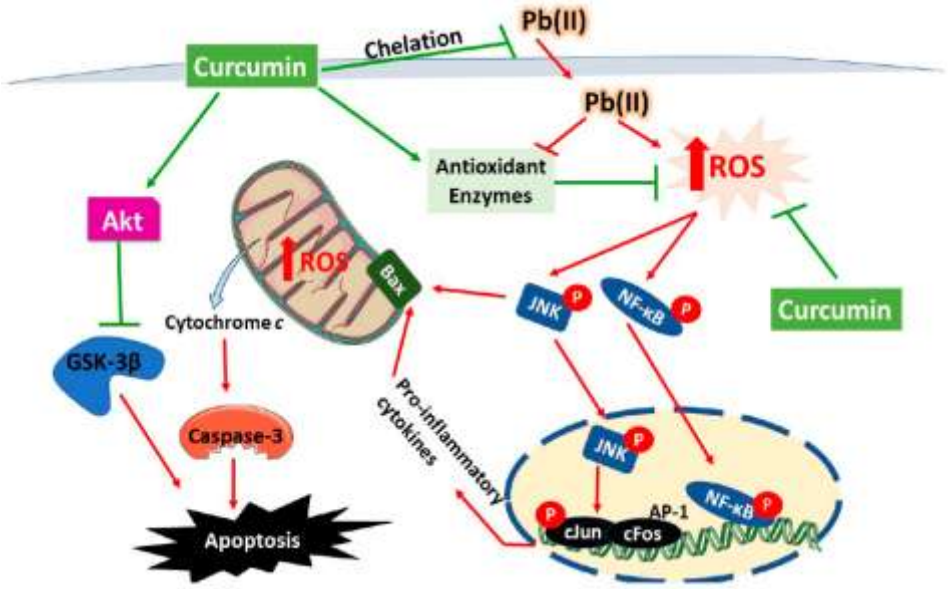

Fig 3:- A schematic diagram illustrating the protective mechanism of curcumin against Pb (II) hepatotoxicity[103].

The study of Allusaini A et al, demonstrates that CUR prevents Pb hepatotoxicity by attenuating oxidative stress, inflammation, DNA damage and cell death.Pb(II) increases ROS generation and activates NF-κB, JNK and GSK-3β, resulting in inflammation and cell death via apoptosis. Curcumin suppresses ROS production, chelates Pb (II), boosts antioxidant defenses and activates Akt signaling. Akt deactivates GSK-3β through phosphorylation at Ser9.[103]Liu L et al. showed that curcumin, in addition to inhibiting NF-κB pathway, activates the Nrf2/HO-1 signaling pathway in a dose- and time-dependent manner, with consequent reduction of TNF-α, IL-1β, and IL-6

levels in vitro, decrease in eosinophil and WBC counts in BAL, and reduction of AHR in a murine model of asthma.[104]The effects of curcumin on pulmonary fibrosis derive from its action on multiple pathways and through multiple mechanisms. As in asthma, the curcumin inhibition of NF-κB has a role in pulmonary fibrosis, by causing a reduction of TNF-α and cyclo-oxygenase 2 (COX-2) levels [105] and TGF-β1 levels [106].Kurup et al used a murine model of latex allergy to investigate the role of curcumin as animmunomodulator. BALB/c mice were exposed to latex allergens and developed latex allergywith a thyroid hormone (Th)2-type immune response.[107]

Grape Seed Extract:

Grape seed proanthocyanidins (GSPs) are promising agents that have antioxidant properties [108] and appear to exhibit minimal toxicity [109]. GSPs are a mixture of polyphenols/flavanols and mainly contain proanthocyanidins (89%), which constitute dimers, trimers, tetramers, and oligomers/polymers of monomeric catechins and/ or (-)-epicatechins[110]. The results from the study of Akhtar S et al showed for the first time the chemotherapeutic efficacy of GSPs in controlling the growth of human NSCLC cells in vitro and tumor xenograft growth in vivo. The in vivo studies show that inhibition of the growth of lung tumor xenografts in nude mice by dietary GSPs is associated with the inhibition of tumor cell proliferation, angiogenesis, and up-regulation of IGFBP 3.[111] The study of Zhou S Y et al evaluated GSPE's effects on airway inflammation and airway remodeling in a chronic asthmatic model. The GSPE treatment markedly decreased interleukin (IL)-4, IL-13, and vascular endothelial growth factor (VEGF) levels in BALF in addition to the total serum IgE levels. A histological examination demonstrated that GSPE significantly ameliorated allergen-induced lung eosinophilic inflammation and decreased PAS-positive epithelial cells in the airway.[112] The study of Ali Asghar Hemmatia et al investigated the effect of grape seed extract on bleomycin-induced lungfibrosis in rat. It was found that grape seed extract was able to diminish the fibrogenic effects of bleomycin on lung. This effect of grape seed can be attributed to activeingredients of the plant with anti-oxidant properties.[113]Grape seed extract (GSE) has antiviral activities against hepatitis A virus (HAV) and human norovirussurrogates (feline calicivirus (FCV-F9) and murine norovirus (MNV-1)).[114]

Stevia:

Stevioside, an abundant component of Stevia rebaudiana leaf, has become well-known for its intensesweetness (250–300 times sweeter than sucrose) and is used as a non-caloric sweetener in several countries. A number of studies have suggested that, beside sweetness, stevioside along with related compounds, which include rebaudioside A (second most abundant component of S. rebaudiana leaf), steviol and isosteviol(metabolic components of stevioside) may also offer therapeutic benefits, as they have anti-hyperglycemic, anti-hypertensive, anti-inflammatory, anti-tumor, anti-diarrheal, diuretic, and immunomodulatory actions. It is of interest to note that their effects on plasma glucose level and blood pressure are only observed when these parameters are higher than normal. As steviol can interact with drug transporters, its role as a drug modulator is proposed.[115]

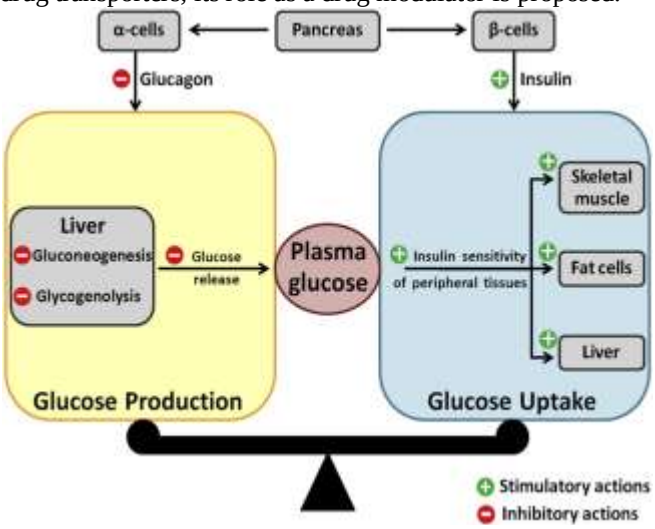

Fig. 4:- The possible anti-hyperglycemic actions of stevioside and related compounds.[115].

Stevioside inhibits glucose production (minus sign) in the fig 4 by inhibiting glucagon secretion fromα cell of pancreas which affects both gluconeogenesis and glycogenolysis, and direct suppression of phosphoenol pyruvate carboxy kinase (PEPCK) activity, a rate limiting enzyme in gluconeogenesis in the liver. All of which causes a

reduction of glucose release from the liver. On the other hand, stevioside, steviol and rebaudioside A stimulate glucose uptake (plus sign) in the fig 4 by increasing insulin secretion from β cell of pancreas and enhancing insulin sensitivity of peripheral tissues promoting glucose uptake. Therefore, they exhibit antihyperglycemic action by reducing glucose production while increasing glucose uptake to maintain plasma glucose balance.[115]Stevia increases the secretion of GIP, insulin, leptin, body weight, and glycaemia but keeps food consumption normal. Sweeteners modulate the hormonal response of cytokines and the proliferation of lymphocytes in the intestinal mucosa.[116]The study of Boonkaewwan, Cet al suggested that stevioside attenuates synthesis of inflammatory mediators in LPS-stimulated THP-1 cells byinterfering with the IKKâand NF-_B signaling pathway, and stevioside-induced TNF-R secretion ispartially mediated through TLR4 thereby elucidating the anti-inflammatory and immunomodulatory activities of stevioside and its metabolite, steviol.[117]

Vitamin A:

Vitamin A is a fat-soluble vitamin, which is crucial for maintaining vision, promoting growth and development, and protecting epithelium and mucosal integrity in the body [118]. It is known to play an important role in enhancing immune function, and having a regulatory function in both cellular and humoral immune responses [118]. Vitamin A supplementation to infants has shown the potential to improve antibody response after some vaccines, including measles [118] and anti-rabies vaccination (2.1 times) [119]. Inaddition, an enhanced immune response to influenza virus vaccination has also been observed in children (2-8 years) who were vitamin A and D-insufficient at baseline, aftersupplementation with vitamin A and D [120].

Vitamin D:

Vitamin D, another fat-soluble vitamin, plays a vital role in modulating both innate andadaptive immune responses [121]. Epidemiological data has linked vitamin D deficiency toincreased susceptibility to acute viral respiratory infections [122]. Recent reviews evaluating possible mechanisms suggest that vitamin D plays an important modulatory role of the innate immune responses to respiratory viral infections, such as Influenza A and parainfluenza 1 and 2, and Respiratory syncytial virus (RSV) [123]. A systematic review on the role of vitamin D in the prevention of acute respiratory infections, which included studies (4 cross-sectional studies, 8 case-control studies, 13 cohort studies and 14 clinical trials), noted that observational studies predominantly reported statistically significant associations between low vitamin D status and increased risk of both upper and lower respiratory tract infections [124]. A study by Aglipay et al. on the effect of high dose (2000 IU/day) vs. standard-dose (400 IU/day) vitamin D supplementation on viral upper respiratory tract infections did not show any significant difference between the two group[125]. However, only about 1/3 of the study population had vitamin D levels <30 ng/ml. A recent RCT on the impact of vitamin D supplementation on influenza vaccine response in deficient elderly person, showed that it promotes a higher TGFβ plasma level without improving antibody production, and suggested that supplementation seems to direct the lymphocyte polarization toward a tolerogenic immune response [126]. Similarly, in another RCT, a monthly high-dose (100,000 IU/month) vitamin D supplementation reduced the incidence of acute respiratory infections in older long-term care residents, in comparison to a standard dose group (12,000 IU/month) [127]. It is evident that the role of vitamin D supplementation on antiviral immunity against respiratory infections is likely to depend on the vitamin D status of the individual. Furthermore, vitamin D has demonstrated a beneficial effect in other viralinfections, for example adding vitamin D to conventionalPeg-α-2b/ribavirin therapy for treatment-naïve patients with chronic HCV genotype 1infection significantly improved the viral response [128], and a similar effect has also beenobserved in patients with HCV genotype 2-3 [129].

Conclusion:-

Many traditional medicinal plants and herbs were reported to have strong antiviral activity. In view of the signification number of plant extracts that have yielded positive results it seems reasonable to concludethat there are probably numerous kinds of antiviral agents in these materials. The traditional use of some of the medicinal plants for the treatment of infectious diseases of viral origin, therefore, is justified. Finally, the development of new medicinal plant products is vital in controlling the threats posed by some pathogenic viruses. Although many synthetic immunomodulatory drugs with various mechanisms of action have been discovered and developed, they failed to be successful clinically due to their toxicity, less bioavailability, and stability problem. Medicinal herbs and their active metabolites deliver alternative potential to ongoing therapy for a wide array of immunological disorders by modulation of the immune response. Research to discover natural products as drug candidates for development of immunomodulatory agents has gained momentum as they offer safer alternatives to conventional therapies.

Nutraceuticals might be defined as substances that have physiological benefits that prevents against chronic diseases and has antiviral property and immunomodulatory effects. Nowadays, nutraceuticals have received considerable interest due to potential nutritional, safety and therapeutic effects. In the present review much effort has been devoted to present new concepts about nutraceuticals based on their diseases modifying indications. Emphasis has been made to present herbal nutraceuticals as its antiviral and immunomodulator properties. The use of nutraceuticals, as an attempt to accomplish desirable therapeutic outcomes with reduced side effects, as compared with other therapeutic agents has met with great monetary success.

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