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RESEARCH ARTICLE

PHENOTYPIC AND MOLECULAR ANALYSIS IN TINOSPORA CORDIFOLIA.

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Abstract

Natural products with medicinal value are gradually gaining importance in clinical research due to their well-known property of no side effects as compared to drugs. Tinospora cordifolia commonly named as "Guduchi" is known for its immense application in the treatment of various diseases in the traditional ayurvedic literature. Recently the discovery of active components from the plant and their biological function in disease control has led to active interest in the plant across the globe. Our present study in this review encompasses (i) the genetic diversity of the plant and (ii) active componen ts isolated from the plant and their biological role in disease targeting. The future scope of the review remains in exploiting the biochemical and signaling pathways affected by the compounds isolated from Tinospora so as to enable new and effective formulation in disease eradication.

Introduction:-

Tinospora cordifolia commonly named as "Guduchi" in Sanskrit belonging to family Menispermaceae is a genetically diverse, large, deciduous climbing shrub with greenish yellow typical flowers, found at higher altitude.[1–3] In racemes or racemose panicles, the male flowers are clustered and female are solitary. The flowering season expands over summers and winters.[4] A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides[4] have been isolated from the different parts of the plant body, including root, stem, and whole plant. Recently, the plant is of great interest to researchers across the globe because of its reported medicinal properties like anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulatory and anti-neoplastic activities. In this review, we focus our attention to: (i) the reported genetic diversity in the Plant (ii) biological roles reported in humans and animals and active components from the plant. (iii) biological roles reported in humans and animals.

Material and Method:-

Published literature on recent developments in research in *Tinospora cordifolia*, including original articles and papers in Pubmed and Pubmed Central Databases were taken into study for the report. Information extracted from a total of 175 published articles of which five review articles and cross references thereof were collected. The search criteria were restricted to the roles of the plant in the field of medical advancements and the effects that has been observed with different experiments.

All the reports of experiments on different model types (*in vitro*, *ex vivo*, and *in vivo*) were taken varying from

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animal and human model systems. Reported data was analysed and represented in the form of figures and tables for the current review. ChemDraw Ultra 9.0 Software, Cambridge soft Life Science Enterprise Solutions was used for drawing the figures in the review. The figures of the compounds were obtained as reported in different journal sources.

Results:-

Tinospora cordifolia: A genetically diverse plant:-

Reports on studies of morphological and physiological characters of the plant, including plant length, stem diameter, growth habit, floral morphology, flower color, stomatal density, trichomal density, lenticels density, petiole length, plant biomass, and other characteristics of the plant and diversity in the genetic components identified by markers have indicated the diversity in the medicinal plant which has profound importance for efficient and effective management of plant genetic resources. Reports using markers for random amplified polymorphic DNA,[5] and inter-simple sequence repeat primers[1,5] have pointed toward the genetic variation within the population. However, reports on conservation strategies and propagation of the germplasm are few.

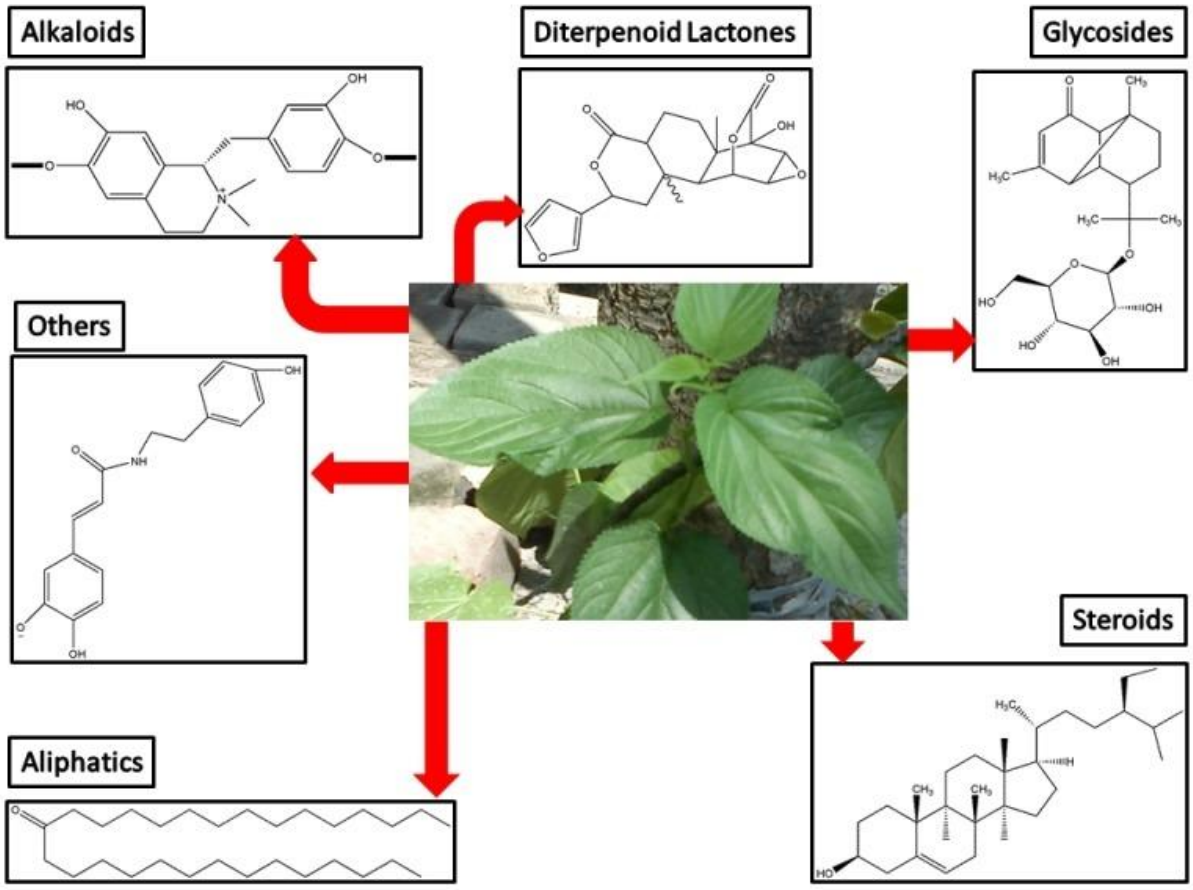
Tinospora cordifolia: Biological roles:-

A myriad of biologically active compounds, including alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds, and polysaccharides have been isolated from different parts of the plant body [Table 1], Figure 1]. These compounds have been reported to have different biological roles in disease conditions thus enabling potential application in clinical research. *Tinospora cordifolia* extracts are extensively used in various herbal preparations for the treatment of different ailments for its anti-periodic, anti-spasmodic, anti-microbial, anti-osteoporotic, anti-inflammatory, anti-arthritic, anti-allergic, and anti-diabetic properties[6] [Table 1].

Table 1

Active components and biological roles in humans and animals

Active component types	Compounds	Source	Reported biological effects in animals	In humans
Alkaloids	Berberine Choline Palmatine Tembetarine Magnoflorine Tetrahydropalmatine Tinosporin Isocolumbin Tetrahydropalmatine Jatrorrhizine Aporphine alkaloids, N-formylasimilobine 2-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside (tinoscorside A, 1) Aporphine alkaloids, N acetylasimilobine 2-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyr	Stem root	Isoquinoline alkaloids have anti-cataract potential in rats. Anti-oxidant activity in mice, anti-cancer in ehrlich ascites carcinoma (EAC) mice, hypoglycemic activity in RINm5F rat insulinoma cell line	Anti-cancer, infections, in immuno-mod Neurological, anti-diabetes



The major biological property of Tinospora cordifolia includes:-

Immunomodulatory property;-

The immuomodulatory property of *Tinospora cordifolia* is well documented. Active compounds 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside and syringin[6] has been reported to have potential immunomodulatory and cytotoxic effects.[13]They have been reported to function by boosting the phagocytic activity of macrophages, production of reactive oxygen species (ROS) in human neutrophil cells, enhancement in nitric oxide (NO) production by stimulation of splenocytes and macrophages indicative of anti-tumor effects. Aqueous *Tinospora* extracts has been also reported to influence the cytokine production, mitogenicity, stimulation and activation of immune effector cells. In mice, *Tinospora cordifolia* extracts has been shown to result in up-regulation of IL-6 cytokine, resulting in acute reactions to injury, inflammation, activation of cytotoxic T cells, and B cell differentiation. Active compounds in aqueous extracts like alkaloids, di-terpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds or polysaccharides[19] in experimental rat model have been reported for their cytotoxic action. Dry stem crude extracts of *Tinospora cordifolia* with a polyclonal B cell mitogen, G1-4A on binding to macrophages have been reported to enhance immune response in mice by inducing secretion of IL-1, together with activation of macrophages. Reports on *Tinospora cordifolia* in prevention of oxidative damage also exist. The (1,4)-alpha-d-glucan (alpha-d-glucan), derived *Tinospora cordifolia* have been shown to activate human lymphocytes with downstream synthesis of the pro- and anti-inflammatory cytokines, *in vitro.* Synergistic effects of compounds in the immunomodulatory activity of *Tinospora cordifolia* are reported.[6]

Anti-diabetes property:-

The stem of *Tinospora cordifolia* is widely used in the therapy of diabetes by regulating the blood glucose in traditional folk medicine of India. It has been reported to mediate its anti-diabetic potential through mitigating oxidative stress (OS), promoting insulin secretion and also by inhibiting gluconeogenesis and glycogenolysis, thereby regulating blood glucose. Alkaloids, tannins, cardiac glycosides, flavonoids, saponins, and steroids as the

major phytoconstituents of *Tinospora cordifolia* have been reported to play an anti-diabetic role.

The isoquinoline alkaloid rich fraction from stem, including, palmatine, jatrorrhizine, and magnoflorine have been reported for insulin-mimicking and insulin-releasing effect both *in vitro* and *in vivo*.[10] Oral treatments of root extracts have been reported to regulate blood glucose levels, enhance insulin secretion and suppress OS markers. Initiation and restoration of cellular defence anti-oxidant markers including superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione (GSH), inhibition of glucose 6-phosphatase and fructose 1, 6-diphosphatase, restoration of glycogen content in liver was reported in *in vitro* studies.[10] The crude stem ethyl acetate, dichloromethane (DCM), chloroforms and hexane extracts of *Tinospora cordifolia* inhibited the enzyme's salivary and pancreatic amylase and glucosidase thus increasing the post-prandial glucose level and finds potential application in treatment of diabetes mellitus.

The root extract has been reported to decrease the levels of glycosylated hemoglobin, plasma thiobarbituric acid reactive substances, hydroperoxides, ceruloplasmin and vitamin E diabetic rats. Oral administration of *Tinospora cordifolia* extract in "Ilogen-Excel" formulation (Ayurvedic herbal formulation) composed of eight medicinal plants including *Curcuma longa*, *Strychnos potatorum*, *Salacia oblonga*, *Tinospora cordifolia*, *Vetivelia zizanioides*, *Coscinium fenestratum*, *Andrographis paniculata*, and *Mimosa pudica* is reported to reduce GSH and vitamin C in blood and urine glucose and lipids in the serum and tissues in alloxan diabetic rats with a subsequent decrease in body weight. Decreased concentration of GSH, GPx, and SOD, catalase activity is reported in heart and brain of diabetic rats. *T. cardifolia* root extract (TCE) has been reported to cause an increase in body weight, total hemoglobin and hepatic hexokinase and lowering hepatic glucose-6-phosphatase, serum acid phosphatase (ACP), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) in diabetic rats thus having hypoglycemic and hypolipidaemic effect.

The protective effects of TCE were reported in presence of higher levels of anti-oxidant molecules and enzymes. TCE has been shown to significantly counterbalance the diabetes-associated OS in the maternal liver by lowering the levels of malondialdehyde and ROS and the increased levels of GSH and total thiols.

Anti-toxic effects:-

Tinospora cordifolia extracts have been reported to scavenge free radicals generated during aflatoxicosis. It exhibited protective effects by lowering thiobarbituric acid reactive substances (TBARS) levels and enhancing the GSH, ascorbic acid, protein, and the activities of anti-oxidant enzymes viz., SOD, CAT, GPx, Glutathione S-transferase (GST) and glutathione reductase (GR) in kidney. Alkaloids such as a choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine from *Tinospora cordifolia* showed protection against aflatoxin-induced nephrotoxicity. *Tinospora cordifolia* stem and leaves extract has shown hepatoprotective effect in Swiss albino male mice against lead nitrate induced toxicity. Oral administration of plant extracts prevented the occurrence of lead nitrate induced liver damage. Decreased level of SOD, CAT and increased level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, and ACP were observed in mice suffering from lead toxicity. Synergistic administration of aqueous extract of stem and leaf along with the lead nitrate increased the activities of SOD and CAT and decreased the levels of AST, ALT, ALP, and ACP enzymes. Protective role of aqueous extract of stem and leaves of *Tinospora cordifolia* overcoming the toxic effects of lead is shown as its effects on the hematological values. Cyclophosphamide (CP) an anti-cancer drug has been reported to reduce the GSH content in both bladder and liver and lowered levels of cytokines Inerferon-γ and IL-2 an increased levels of pro-inflammatory cytokine TNF-α. This effect could be reversed on *Tinospora cordifolia* treatment indicating the role of *Tinospora cordifolia* in overcoming CP induced toxicities in cancer treatment.

Anti-arthritic, anti-osteoporotic effects:-

Single or synergistic formulations of *Tinospora cordifolia* with *Zingiber officinale* has been used in rheumatoid arthritis treatment in traditional medicine. *Tinospora cordifolia* have been reported to affect the proliferation, differentiation and mineralization of bone like matrix on osteoblast model systems *in vitro* and hence finds potential application as an anti-osteoporotic agent. Alcoholic extract of *Tinospora cordifolia* have been shown to stimulate the growth of osteoblasts, increasing the differentiation of cells into osteoblastic lineage and also increasing the mineralization of bone like matrix. Ecdysteroids isolated from the plant have been reported of protein anabolic and anti-osteoporotic effects in mammals. Beta-Ecdysone (Ecd) from *Tinospora cordifolia* extracts have been reported to induce a significant increase in the thickness of joint cartilage, induce the osteogenic differentiation in mouse mesenchymal stem cells and to relieve osteoporosis in osteoporotic animal models. Further 20-OH-β-Ecd isolated

from *Tinospora cordifolia* has been reported of its anti-osteoporotic effects thus highlighting the role of *Tinospora cordifolia* in the treatment of osteoporosis and osteoarthritis.

Anti-HIV effects:-
TCE has been shown to demonstrate a decrease in the recurrent resistance of HIV virus thus improving the therapeutic outcome. Anti-HIV effects of TCE was revealed by reduction in eosinophil count, stimulation of B lymphocytes, macrophages and polymorphonuclear leucocytes and hemoglobin percentage thus, revealing its promising role of application in management of the disease.

Anti-cancer effects:-
The anti-cancer effects of *Tinospora cordifolia* are mostly studied in animal models. TCE have been shown to have a radioprotective role by significantly increase in body weight, tissue weight, testes-body weight ratio and tubular diameter and inhibit the harmful effects of sub-lethal gamma radiation on testes in male Swiss albino mice. In pre-irradiating mice, TCE significantly affected radiation induced rise in lipid peroxidation and resulted in the decline of GSH concentration in testes. Pre-treatment of HeLa cells by TCE have been shown to decrease the cell viability, increase LDH and decrease in GSH S-transferase activity. Dihydrotestosterone (DHT) in TCE has been reported to stimulate the growth and proliferation of Human LNCaP cells (which are androgen-sensitive human prostate adenocarcinoma cells). Androgenic compounds in TCE act via androgen receptor. Newly isolated compounds like (5R, 10R)-4R, 8R-dihydroxy-2S, 3R: 15, 16-diepoxycleroda-13 (16), 17, 12S: 18,1S-dilactone (ECD), a diterpenoid from *Tinospora cordifolia* has been reported for its chemopreventive potential in diethylnitrosamine (DEN) induced hepatocellular carcinoma (HCC) in rats by decreasing anti-oxidant activities via SOD, CAT and detoxification enzymes like GSH, GPx and subsequent increase in the activities of the hepatic markers ((Serum glutamic oxaloacetic transaminase)SGOT, (Serum Glutamic Pyruvate Transaminase) SGPT, LDH) and decreased serum transaminase level thus confirming its anti-tumor effects and promising application as a potent chemo preventive drug for HCC.[26]

The radiosensitizing activity of DCM extract of *Tinospora cordifolia* has been reported in Ehrlich ascites carcinoma (EAC) mice enabling tumor-free survival via depletion of GSH and glutathione-S-transferase by elevated levels of lipid peroxidation and DNA damage to tumor cells. TCE hexane fraction has been shown to block the G1 phase in EAC mice and cause apoptosis by the formation of apoptotic bodies, nuclear condensation, activation of caspase-3, decreased cell number and ascites volume, increased expression of pro-apoptotic gene, *Bax*, and decreased expression of anti-apoptotic gene, *Bcl-2*. TCE could induce a reduction of papillomas, tumor yield, tumor burden, and tumor weight while increase phase II detoxifying enzymes in skin carcinoma animal models. The effect of a hydroalcoholic (80% ethanol: 20% distilled water) extract of aerial roots of *Tinospora cordifolia* on Swiss albino mice revealed a significant increase in acid-soluble sulfhydryl (-SH), cytochrome *P* (450) contents, and enzyme activities of cytochrome *P* (450) reductase, cytochrome b5 reductase, GST, DT-diaphorase (DTD), SOD, catalase, GPX, and GR activity in the liver highlighting the chemopreventive role of *Tinospora cordifolia* against carcinogenicity.

In vivo anti-angiogenic activity of TCE in B16-F10 melanoma was detected by increased levels of pro-inflammatory cytokines, including IL-1 β, IL-6, TNF-α, granulocyte monocyte-colony stimulating factor (GM-CSF) and the vascular endothelial cell growth factor (VEGF), increased production of anti-angiogenic agents IL^{-2} and tissue inhibitor of metalloprotease-1 (TIMP-1) in the B16-F10 extract-treated animals. The polysaccharide fraction from *Tinospora cordifolia* was found to be very effective in reducing the metastatic potential of B16-F10 melanoma cells. Markers of neoplastic development were reduced significantly in the treated animals compared with the untreated control animals. Most of the synthetic chemotherapeutic agents suffer from toxic side effects.[The effect of Guduchi extracts was comparable or better than doxorubicin treatment.

Tinospora cordifolia: Anti-microbial activity:-
The methanol extracts of *Tinospora cordifolia* have been reported to have potential against microbial infections. The anti-bacterial activity of *Tinospora cordifolia* extracts has been assayed against *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella flexneri, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter aerogene*, and *Serratia marcesenses* (Gram-positive bacteria). In mice models, TCE has been reported to function in bacterial clearance and improved phagocytic and intracellular bactericidal capacities of neutrophils. TCE has been reported of immunostimulant properties on macrophages. Intra-mammary infusion of hydro-methanolic extracts of *Tinospora cordifolia* treatment

showed enhanced phagocytic activity of polymorphonuclear cells in bovine subclinical mastitis.

Tinospora cordifolia: Anti-oxidant activity:-

The anti-oxidant capacity of *Tinospora cordifolia* stem methanol extracts administered orally increased the erythrocytes membrane lipid peroxide and catalase activity. It also decreased the activities of SOD, GPx in alloxan-induced diabetic rats. *Tinospora cordifolia Willd.*(Menispermaceae) extracts possess possible inhibitors of aldose reductase and anti-oxidant agents thereby reducing chemotoxicity induced by free radicals.

TCE has been reported of its strong free radical scavenging properties against superoxide anion (O_2^-), hydroxyl radicals (OH), NO radical, and peroxynitrite anion ($ONOO^-$). The extract was also found to reduce the toxic side effects of CP in mice by the free radical formation. *Tinospora cordifolia* lowers the levels of malondialdehyde and ROS and the higher levels of GSH and total thiols. The protective effects of *Tinospora cordifolia* could be observed even in the fetal milieu, with higher levels of anti-oxidant molecules and enzymes.

Tinospora cordifolia has the ability to scavenge free radicals generated during aflatoxicosis. *Tinospora cordifolia* showed protection against aflatoxin-induced nephrotoxicity due to the presence of alkaloids such as a choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine.[8] A significant increase in the concentration of TBARS in brain along with a decrease in heart has been observed in diabetic rats.It also enhanced formation of SOD, GPx, and GSH in liver. Treatment with *Tinospora cordifolia* also inhibited glucose 6-phosphatase and fructose 1, 6-diphosphatase; and restored glycogen content in liver. *Tinospora cordifolia* has been shown to regulate blood glucose (5R, 10R)-4R, 8R-dihydroxy-2S, 3R: 15, 16-diepoxycleroda-13 (16), 17, 12S: 18,1S-dilactone (ECD), a diterpenoid from *Tinospora cordifolia* has been shown to possess chemo-preventive potential in DEN induced HCC rats. Treatment of ECD in both preventive and curative DEN induced animals increased the level of anti-oxidants and detoxification enzymes.[26]

An aqueous extract of *Tinospora cordifolia* has a radio-protective enhancing the survival of mice against a sub-lethal dose of gamma radiation. *Tinospora cordifolia* was effective in elevating the GSH levels, expression of the gamma-glutamylcysteine ligase and Cu-Zn SOD genes. Aqueous extract of *Tinospora cordifolia* inhibited radiation mediated 2-deoxyribose degradation by inhibiting the formation of (Fe^{2+})-bipiridyl complex formation to confer radio-protective effects.

The arabinogalactan polysaccharide (TSP) isolated from *Tinospora cordifolia* showed good protection against iron-mediated lipid peroxidation of rat brain homogenate as revealed by the TBARS and lipid hydroperoxide (LOOH) assays.

Tinospora cordifolia also has the components that decrease the recurrent resistance of HIV virus to antiretroviral therapy (ART) and improve the outcome of the therapy. The effect of a hydroalcoholic (80% ethanol: 20% distilled water) extract of aerial roots of *Tinospora cordifolia* on carcinogen/drug metabolizing phase-I and phase-II enzymes, anti-oxidant enzymes, GSH content, LDH and lipid peroxidation has been shown in liver of Swiss albino mice. The enhanced GSH level and enzyme activities involved in xenobiotic metabolism and maintaining anti-oxidant status of cells are suggestive of a chemo-preventive efficacy of *Tinospora cordifolia*.

Tinospora cordifolia has been reported to contain an alpha-glucosidase inhibitor, characterized as saponarin (apigenin-6-C-glucosyl-7-O-glucoside). The leaf extract had appreciable anti-oxidant and hydroxyl radical scavenging activities. Pepticare, a herbomineral formulation of the Ayurveda medicine consisting of the herbal drugs: *Glycyrrhiza glabra, Emblica officinalis* and *Tinospora cordifolia*, has anti-ulcer and anti-oxidant activity in rats.

Hyponidd is another herbomineral formulation composed of the extracts of 10 medicinal plants (*Momordica charantia, Melia azadirachta, Pterocarpus marsupium, Tinospora cordifolia, Gymnema sylvestre, Enicostemma littorale, Emblica officinalis, Eugenia jambolana, Cassia auriculata* and *Curcuma longa*). Hyponidd administration also decreased levels of glycosylated hemoglobin, plasma thiobarbituric acid reactive substances, hydroperoxides, ceruloplasmin and alpha-tocopherol in diabetic rats.

Anti-oxidant activities of Dihar, a polyherbal formulation containing drugs from eight different herbs viz., *Syzygium cumini, Momordica charantia, Emblica officinalis, Gymnema sylvestre, Enicostemma littorale, Azadirachta indica,*

Tinospora cordifolia and *Curcuma longa* in streptozotocin induced type 1 diabetic rats. Dihar produced a significant decrease in serum creatinine and urea levels in diabetic rats.[7]

Tinospora cordifolia: Effects on other diseases:-

A dose dependent reduction in infarct size and in lipid peroxide levels of serum and heart tissue were observed with the prior treatment of *Tinospora cordifolia*. The activation of macrophages by cytotoxic T cells leads to increase in GM-CSF which leads to leucocytosis and improved neutrophil function. Octacosanol isolated from *Tinospora cordifolia* inhibits proliferation of endothelial cells and Ehrlich ascites tumor cells, inhibits neovascularization induced by angiogenic factors in chick chorioallantoic membrane and rat cornea *in vivo* angiogenesis assays and also inhibits secretion of ascites fluid in the growing tumor cells *in vivo*[33] by inhibiting activity of matrix metalloproteinases (MMPs) and translocation of transcription factor nuclear factor-kappa-B (NF-κB) to nucleus. Oral administration of 70% methanolic extract of *Tinospora cordifolia* stem reduces sperm motility and density, lowering of serum testosterone, protein, sialic acid, glycogen contents, and depletion of vesicular fructose of testes leading to reduction of male fertility in rats. The *in vivo* administration of alcoholic extract of *Tinospora cordifolia* has been reported to increase bone marrow derived macrophages (BMDM) in bearing Dalton's lymphoma (DL). The polyherbal preparations Caps HT2 of *Tinospora cordifolia*, could reduce plasma recalcification time and enhanced the release of lipoprotein lipase enzyme. Other polyherbal HP-1 has hepatocurative and anti-oxidant efects.

Discussion:-

Tinospora cordifolia has an importance in traditional ayurvedic medicine used for ages in the treatment of fever, jaundice, chronic diarrhea, cancer, dysentery, bone fracture, pain, asthuma, skin disease, poisonous insect, snake bite, eye disorders.[2] Recent reports have shown the compounds and their biological roles in *Tinospora cordifolia* extract. Such properties may be exploited for production of new formulations, which may be better and promising over conventional one. Although genetically diverse and reports of application of tissue culture based propagation of Tinospora exist, effective conservation strategies of the germplasm for such an economically important medicinal plant with many biological role remains yet to be accomplished.

Conclusion:-

A plant with as diverse a role as *Tinospora cordifolia* is a versatile resource for all forms of life. There are reports as already discussed that the plant extracts have active compounds in the form of alkaloids, glycosides, lactones and steroids. All these active compounds have immunomodulatory and physiological roles of different types, thereby demonstrating the diverse versatility of the plant. Studies need to be conducted with aspects how the active compounds actually interact with the living systems and affects the structure-function relationships. Crystal structures of the membrane bound receptors and the activation of the downstream signaling cascades and the changes in the immediate environment of the site of action can lead us into identification of novel perspectives into our understanding of nature. The search into the vivacious sources of nature can also lead us into differential interactions among the evolutionarily related groups of organisms. The future scope of the review remains in exploiting the biochemical and signaling pathways of the active components of *Tinospora* thus, enabling effective disease targeting. With so much to offer to the scientific world of medicine, the plant Tinosporia truly acts as an incredible source.

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