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TINOSPORA CORDIFOLIA

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ABSTRACT

The active principles of Tinospora cordifolia a traditional Indian plant were found to possess anticomplementary and immunomodulatory activities. Syringin (TC-4) and cordiol (TC-7) inhibited the in vitro immunohaemolysis of antibody-coated sheep erythrocytes by guinea pig serum. The reduced Immunohaemolysis was found to be due to inhibition of the C3-convertase of the classical complement pathway. However, higher concentrations showed constant inhibitory effects. The compounds also gave rise to significant increases in IgG antibodies in serum. Humoral and cell-mediated immunity were also dose-dependently enhanced. Macrophage activation was reported for cordioside (TC-2), cordiofolioside A (TC-5) and cordiol (TC-7) and this activation was more pronounced with increasing incubation times.

INTRODUCTION

Natural products and [1]traditional medicines are of great importance. Such forms of medicine as traditional Chinese medicine, Ayurveda, Kampo, traditional Korean medicine, and Unani have been practiced in some areas of the world and have blossomed into orderly-regulated systems of medicine. This study aims to review the literature on the relationship among natural products, traditional medicines, and modern medicine, and to explore the possible concepts and methodologies from natural products and traditional medicines to further develop drug discovery. The unique characteristics of theory, application, current role or status, and modern research of eight kinds of traditional medicine systems are summarized in this study. Although only a tiny fraction of the existing plant species have been scientifically researched for bioactivities since 1805,when the first Pharmacologically-Active compound morphine was isolated from opium, natural products and traditional Medicines have already made fruitful contributions for modern medicine. When used to develop new drugs, natural products and traditional medicines have their incomparable advantages, such as abundant clinical experiences, and their unique diversity of chemical structures and biological activities. Since prehistoric times, [2]humans have used natural products, such as plants, animals, microorganisms, and marine organisms, in medicines to alleviate and treat diseases. According to fossil records, the human use of plants as medicines may be traced back at least 60,000 years. The use of natural products as medicines must, of course, have presented a tremendous challenge to early humans. It is highly probable that when seeking food, early humans often consumed poisonous plants, which led to vomiting,

diarrhea, coma, or other toxic reactions—perhaps even death. However, in this way, early humans were able to develop knowledge about edible materials and natural medicines. Subsequently, humans invented fire, learned how to make alcohol, developed religions, and made technological breakthroughs, and they learned how to develop new drugs. Traditional medicines (TMs) make use of natural products and are of great importance. Such forms of medicine as traditional Chinese medicine (TCM), Ayurveda, Kampo, traditional Korean medicine (TKM), and Unani employ natural products and have been practiced all over the world for hundreds or even thousands of years, and they have blossomed into orderly-regulated systems of medicine. In their various forms, they may have certain defects, but they are still a valuable repository of human knowledge.

In the case of China, Western medicine was introduced in the sixteenth century, but it did not undergo any development until the nineteenth century. Before that, TCM was the dominant form of medical care in the country. Now TCM still plays an important role in China, and it is constantly being developed. TCM is based on 5000 years of medical practice and experience, and is rich in data from "clinical experiments" which guarantee its effectiveness and efficacy. It has developed techniques with respect to such areas as correct dosage, methods of preparing and processing materials, and the appropriate time to collect the various medicinal parts of plants. It is notable that there is increasing convergence between TCM and modern medicine. With the development of modern technology, it has become possible to determine the pharmacology and mechanisms of action of many Chinese herbs, and TCM has become comprehensible in terms of modern medicine. With advances in the theoretical background, therapeutic principles, associated technologies, and understanding of the life sciences, a clearer understanding of the active compounds of TCM has become possible. At the [3]beginning of the nineteenth century, the era of "modern" drugs began. In 1805, the first pharmacologically-active compound morphine was isolated by a young German pharmacist, Friedrich Sertürner, from the opium plant. Subsequently, countless active compounds have been separated from natural products. Among them, some follow their traditional uses and the others do not. Later, the development of synthetic techniques led to a significant reduction in the importance of natural products, and there were concerns that the use of some natural products for medicinal purposes might be completely banned. However, natural products are important for the development of new drugs, and these products have been in constant use. Some type of medicines, such as anticancer, antihypertensive, and antimigraine medication, have benefited greatly from natural products. The development of new drugs relying purely on modern technology appears to be reaching something of a limit. In developing new drugs, the pharmaceutical industry has tended to adopt high-throughput synthesis and combinatorial chemistry-based drug development since the 1980s; however, the considerable efforts made in this direction have not resulted in the expected drug productivity. Some large pharmaceutical companies are facing great challenges to develop new products. Over the past dozen years, increasing attention has accordingly been paid to natural products in the search for novel drugs in combination with new technology, such as high-throughput [4]selection. Natural products, which have evolved over millions of years, have a unique chemical diversity, which results in diversity in their biological activities and drug-like properties. Those products have become one of the most important resources for developing new lead compounds and scaffolds. Natural products will undergo continual use toward meeting the urgent need to develop effective drugs, and they will play a leading role in the discovery of drugs for treating human diseases, especially critical diseases.

Traditional Medicines:

TM is the oldest form of health care in the world and is used in the prevention, and treatment of physical and mental illnesses. Different societies historically developed various useful healing methods to combat a

variety of health- and life-threatening diseases. TM is also variously known as complementary and alternative, or ethnic medicine, and it still plays a key role in many countries today.The medicaments used in TM are mostly derived from natural products. In TM, "clinical trials" have been conducted since ancient times. In the case of TCM, considerable experience and advances have been accumulated and developed over the past thousands of years with respect to methods of preparation, selection of herbs, identification of medicinal materials, and the best time for obtaining various different plants. Appropriate processing and dose regulation are urgently needed in TCM to improve drug efficacy and reduce drug toxicity. Considerable amounts of data have been acquired through clinical experiments, and in this way TM has assisted in the development of modern drugs. [5]Through its use of natural products, TM offers merits over other forms of medicine in such areas as the following: discovery of lead compounds and drug candidates; examining drug-like activity; and exploring physicochemical, biochemical, pharmacokinetic, and toxicological characteristics. If any form of TM is applied successfully, it may surprisingly assist in the development of new drugs, thereby resulting in many benefits, such as significant cost reductions. TCM is now an inseparable part of the Chinese public health system. In recent years, TCM has gradually gained considerable approval as a complementary or alternative medicine in Western countries. Chinese herbal medicine, which is the most important component of TCM, is currently used in the health care of an estimated 1.5 billion people worldwide. It should be noted that in TCM, several herbs and ingredients are combined according to strict rules to form prescriptions, which are referred to as formulas (*fang ji* in Chinese). Commonly, a classic formula is composed of four elements—the "monarch", "minister", "assistant", and "servant"—according to their different roles in the formula, each of which consists of one to several drugs. Ideally, these drugs constitute an organic group to produce the desired therapeutic effect and reduce adverse reactions. Kampo is the TM of Japan. Between the fifth and sixth centuries, TCM was introduced to Japan from China; since then, [6]TCM has been significantly altered and adapted by Japanese practitioners to meet their particular circumstances and gradually evolved into Kampo. A recent study has found that some physicians in Japan use Kampo medicines in their daily practice—sometimes as the preferred medication. Together with radiotherapy or chemotherapy, some Japanese physicians frequently utilize Kampo medicines in treating cancer patients. This indicates how modern Western medicine can be well integrated with TM. As the use of Kampo continues to rise in conjunction with Western medicine, there is growing realization of the urgent need to study the interactions between these two types of medicines.Unani is an ancient Greek holistic medical system with a history that can be traced back 2500 years. Since the mid-1970s, when the WHO began to place a greater focus on TM, Unani has attracted considerable attention all over the world, especially in India, where it has been integrated into the national health care system. It was reckoned by WHO that a large quantity of people in the world still depend on TMs for health care. [7]The current status of TM differs in different countries. In 2012, the total value of the TCM industry was equivalent to around one-third of the total for China's pharmaceutical industry. It has been determined that 80% of the population in Africa makes use of TM—either alone or in conjunction with conventional medicine. By contrast, traditional Aboriginal medicine in Australia is in danger of vanishing owing to the prevalence of conventional medicine. In the case of Israel with its ethnic diversity, modern medicine is prevailing, and TM is declining. Many practitioners of Western medical science think such TM systems as being short of reliability; however, they are adopted by the majority of people in the world. It is possible to produce remarkable synergy and yield great benefits in developing reformed medicines and new drugs by connecting powerful modern scientific techniques and methods with the reasonable ethnobotanical and ethnomedical experiences of TM.

Drug development from Traditional medicine- Uses- TM is too valuable to be ignored in the research and development of modern drugs. Though it has an enigmatic character, there are also wide contexts for its use in terms of non-Western medical technology or activities. In TM, a single herb or formula may contain many phytochemical constituents, such as alkaloids, terpenoids, flavonoids, *etc.* Generally speaking, these chemicals function alone or in conjunction with one another to produce the desired pharmacological effect. It is notable that a lot of plant-originated drugs in clinical medicine today were derived from TM. In addition, it has been demonstrated that the many valuable drugs derived from plants were discovered through their application in[8]TM. Almost 20 years ago, a thorough investigation of the pharmacopoeias of developed and developing nations and the associated world scientific literature was conducted as part of the WHO's TM Program. The aim of that study was to determine whether TM really had inspired modern drug discoveries and whether there was any correlation between the current use of various compounds and their application in TM. The study focused on various compounds used in drugs derived from plants in different countries, and it established that TM had indeed played a significant role in developing effective new drugs. That study focused on 122 compounds, 80% of which were found to be related to pharmaceutical effects in folk medicine, and it was determined that these compounds originated from 94 plant species. The acceptability, convenience, and accessibility of TMs have been, and will be, helpful for new drug research. As noted above, artemisinin and other antimalarial drugs are examples of modern drugs based on TMs. Early in China's Jin Dynasty, Doctor Hong Ge (AD 284–384) recorded the efficacy and related details of *Artemisia annua* L. in treating malaria in his book *Zhou Hou Bei Ji Fang*. That is the earliest record anywhere of treating malaria with *Artemisia annua* L., and it shows that Chinese physicians 1700 years ago had reached a sophisticated level of medical treatment. Artemisinin is known as *qinghaosu* in Chinese, and its study has made significant progress, including the synthesis of new artemisinin analogs and derivatives, and research efforts into the biological activities and related mechanisms. As a result, artemisinin, as well as its effective derivatives, are extensively applied throughout the world as new-type anti-malarial drugs.The discovery of artemisinin can be traced back to the 1960s, when tropical malaria was a serious problem during the Vietnam War. North Vietnam requested China to help tackle the malaria problem. The Chinese government approved a project for malaria control and drug research in 1967. The research group made its investigations and carried out a large-scale search of the literature on the subject. As part of the phytochemical and pharmacological research effort, a lot of Chinese herbal medicines were screened and investigated with respect to their toxicity or efficacy. Eventually artemisinin was derived from *Artemisia annua* L. in 1972. [9]Artemisinin is quite different from previously-used antimalarial drugs, such as Chloroquine, in that it has a novel structure, with a sesquiterpene lactone bearing a peroxy group, and it does not contain nitrogen heterocycles. Compared with previous antimalarial drugs, artemisinin has the merit of high efficiency, quick effect, and low toxicity. Artemisinin is effective in treating various forms of malaria, such as falciparum and cerebral malaria, which are resistant to chloroquine, and its mechanism of action is different from traditional antimalarial drugs. The discovery of artemisinin was a great success for TCM at a special period in China's history, and it was achieved through a well-organized team of hundreds of researchers. Since that breakthrough, scientists have conducted comprehensive research in such areas as pharmaceutical chemistry, organic synthetic chemistry, and chemical biology. Through etherification and esterification, they have produced a series of well-known new drugs, such as artemether and artesunate. Those drugs have improved efficacy and solubility, which are of benefit for patients receiving oral or intravenous administration and have overcome the high parasite recrudescence rate and low solubility of artemisinin. Most importantly, one of these

scientists, Youyou Tu, was just awarded the 2015 Nobel Medicine Prize for her significant devotion in discovering artemisinin.

Natural Products:

Natural products have a wide range of diversity of multi-dimensional chemical structures; in the meantime, the utility of natural products as biological function modifiers has also won considerable attention. Subsequently, they have been successfully employed in the discovery of new drugs and have exerted a far-reaching impact on chemicobiology. From the past century, the high structural diversity of natural products have been realized from the perspective of physical chemistry. [10]Their efficacy is related to the complexity of their well-organized three-dimensional chemical and steric properties, which offer many advantages in terms of efficiency and selectivity of molecular targets. As a successful example of drug development from natural products, artemisinin and its analogs are presently in wide use for the anti-malaria treatment. This shows how research using natural products has made a significant contribution in drug development. Among anticancer drugs approved in the time frame of about 1940–2002, approximately 54% were derived natural products or drugs inspired from knowledge related to such. For instance, the Vinca alkaloids from *Catharanthus roseus*, and the terpene paclitaxel from *Taxus baccata*, are among successful anticancer drugs originally derived from plants. During the period between 1981 and 2002, the application of natural products in the development of new drugs—especially in the search for novel chemical structures—showed conspicuous success. In that 22-year time frame, drugs derived from natural products have been significant.That is especially true in the case of antihypertensives, where about 64% of newly-synthesized drugs have their origins in natural product structures. Considering their incomparable chemical diversity and novel mechanisms of action, natural products have continued to play a pivotal role in many drug development and research programs. With time, those natural products have undergone interesting and meaningful developments in their ability to interact with numerous, varied biological targets, and some have become the most important drugs in health care system. For example, plants, microorganisms, and animals manufacture small molecules, which have played a major role in drug discovery. Among 69 small-molecule new drugs approved from 2005 to 2007 worldwide, 13 were natural products or originated from natural products, which underlines the importance of such products in drug research and development.

Over the past 50 years, there has been a great diversity of new drugs developed using high-throughput screening methods and combinatorial chemistry; however, natural products and their derived compounds have continued to be highly-important components in pharmacopoeias. Of the reckoned 250,000–500,000 existing plant species, only a tiny proportion has been scientifically researched for bioactivities. Therefore, there is great potential for future discoveries from plants and other natural products which, thus, offer huge potential in deriving useful information about novel chemical structures and their new types of action related to [11]new drug development.

Drug development from natural medicine:

In clinical practice in China in the 1960s, it was found that *Schisandra chinensis* (Turcz.) Baill.—a traditional Chinese herb—had obvious enzyme-reducing and hepatoprotective effects. Chinese scientists then began isolating the chemical constituents of *S. chinensis*. In the subsequent total chemical synthesis and pharmacodynamic study of schisandrin C (which is one of the compounds of *S. chinensis*), researchers found that the intermediate compound bifendate had a stronger pharmacological activity and that the cost of preparation was low. They discovered that it may be used to lower the enzyme content in the treatment of hepatitis B virus. Since the end of the 1980s, chemists and pharmacologists at the Chinese Academy of Medical Sciences have been closely cooperating in studying the structure and activity relationships of bifendate and its analogs. As part of their research, a series of novel derivatives were synthesized. After

screening using a number of chemical and pharmaceutical liver injury models, it was found that the hepatoprotective activities of the derivatives were closely related to the locations of dimethylenedioxy in two benzene rings, the length of the side-chain carboxylic acid, and the heterocycle between the two benzene rings. Finally, a new compound, bicyclol—formulated as 4,4″-dimethoxy-5,6,5′,6′-bis(methylene-dioxy)-2-hydroxy-methyl-2′-methoxycarbonyl biphenyl—was designed and synthesized. Bicyclol had greater *in vivo* absorption, and better bioavailability and biological activity, than bifendate owing to the introduction of the 6-hydroxymethyl group and 6′-carbomethoxy in the side chain. [12]Pharmacological results of bicycle showed antifibrotic and hepatoprotective effects against liver injury and liver fibrosis induced by CCl4 or other hepatotoxins in mice and rats; it also exhibited the antihepatitis virus effect in the 2.2.15 cell line and duck model with viral hepatitis. In clinical trials, it was found that the increased levels of serum alanine aminotransferase and aspartate aminotransferase were dramatically decreased by bicyclol. It was also found that bicyclol prohibited hepatitis B virus replication in chronic hepatitis B patients. Compared with previous anti-hepatitis drugs, bicyclol exhibited a more consolidated effect after the drug was discontinued; the rebound rate was low, with fewer adverse reactions and higher oral bioavailability. Based on previous studies in such areas as synthesis, pharmacology, toxicology, pharmacokinetics, preparation, and quality control, researchers determined that the new antihepatitis drug bicyclol offered significant hepatoprotective effects, antihepatitis virus activity, and fewer adverse reactions. Bicyclol has been approved for the treatment of chronic viral hepatitis in China since 2004. Bicyclol has independent intellectual property rights and belongs to Class 1 of China's New Chemical Drug. The drug is one of the anti-inflammatory and hepatoprotective drugsrecommended by the "Guidelines on Liver Disease Clinical Diagnosis and Treatment" in China, and it has been exported to many countries.In the same decade in which Chinese scientists found that *S. chinensis* (Turcz.) Baill. Had obvious enzyme-reducing and hepatoprotective effects, a program screening for cancer drugs from plants began in 1960 at the National Cancer Institute in the United States. Neither China nor the United States knew what the other was doing in this area. In that US project, 650 plant samples were gathered in three states. After the initial cytotoxicity tests were carried out using crude extracts, *Taxus brevifolia* was chosen for further research. Taxol was isolated as a new compound from *T. Brevifolia*. Taxol has an unusual chemical structure and radically distinctive mechanism of action and was developed as a novel anticancer drug in subsequent decades. Nevertheless, the drug attracted little attention during the early stage of its development because of its poor solubility in water, low yield from natural products, and other disadvantages, particularly by the medical society. The story of Taxol involved many events that nearly resulted in discontinuation of the research. Fortunately, it underwent extraction, isolation, and structural determination; its activity against solid tumors and its mechanism of action were established, and it became developed for clinical practice. Finally, Taxol was approved by the US Food and Drug Administration for treating ovarian cancer in 1992—21 years after the initial breakthrough paper recording its isolation and structural identification. Taxol has remained a basic drug for treating various forms of cancer, and is still being used to develop new synergistic groups of anticancerdrugs.

TINOSPORA CORDIFOLIA

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. In racemes or racemose panicles, the male flowers are clustered and female are solitary. The flowering season expands over summers and winters. A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant. [13]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.

Genetically Diversity:

Reports on studies of [14]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, and inter-simple sequence repeat primers have pointed toward the genetic variation within the population. However, reports on conservation strategies and propagation of the germplasm are few.

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. These compounds have been reported to have different biological roles in disease conditions thus enabling potential application in clinical research. [15]*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

1. Immunomodulatory property:

The immuomodulatory property of [16]Tinospora Cordifolia is well documented. Active compounds 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside and syringin has been reported to have potential immunomodulatory and cytotoxic effects. They have been reported to function by boosting the phagocytic activity of macrophages; production of reactive oxygen extracts 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 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 polysaccharidesin 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.

2. Anti-diabetic activity:

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[17] 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*. [18]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. 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. [19]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.

3. Anti-toxic activity:

Anti- arthritic & anti-osteoporotic:

Single or synergistic formulations of *Tinospora Cordifolia* with zingiber officinalehave 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. [20]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.

4. Anti-HIV activity: 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 [21]management of the disease.

5. Anti-cancer activity: The [22]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. [18]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. The [23]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 [24]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. [25]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.

6. Anti-microbial activity:

The methanol extracts of *Tinospora cordifolia* have been reported to have potential against microbial infections.[26]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.

7. Anti-oxidant activity: The anti-oxidant capacity of *Tinospora cordifolia* stem methanol extracts administered orally increased the erythrocytes membrane lipid peroxide and catalase activity. [21]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 (O2-), 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. [27] *Tinospora cordifolia* showed protection against aflatoxin-induced nephrotoxicity due to the presence of alkaloids such as a choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine. 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 [28]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. 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 (Fe2+)-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). [28]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. Hyponid is another herb mineral 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*). Hyponid 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. 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. [29]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 thegrowing tumor cells *in vivo* 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[30]effects.

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, asthma, skin disease, poisonous insect, snake bite, eye disorders. 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. With so much to offer to the scientific world of medicine, the plant Tinosporia truly acts as an incredible source.

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