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REVIEW ARTICLE

2 Tinosporacordifolia: A Potential Plant with Immunomodulatory Activity

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8 ABSTRACT

Immunomodulation is a procedure, which can alter the immune system of an organism by interfering its 10 function. Modulation of immune system may result in suppression or stimulation of immunological 11 reactivity. Recently the effect of immunomodulators in the treatment of various diseases is significant. 12 Tinosporacordifolia is a widely used shrub in ayurvedic system of medicine. It is reported to benefit the 13 immune system in a variety of ways. The medicinal properties incorporated with this plant are anti-14 diabetic, hypolipidemic, anti-neoplastic, anti-oxidant, anti-inflammatory, immunomodulatory, cognitive, 15 adaptogenic, aphrodisiac, cardioprotective and hepatoprotective effect. Many compounds belonging to 16 different classes such as alkaloids, diterpenoids, phenol, aliphatic compounds and polysaccharides have 17 been isolated from this plant. But it is not well known that which of these compounds are responsible for 18 various activities. Therefore, it needs further exploration of its components, pharmacological action and 19 mechanism of action. This review presents a detail survey of literature on immunomodulatory properties 20 of T.cordifolia. The main aim of the survey is to reinforce scientific reconfirmation of its immunological 21 activities and human studies.

22 Keywords: Immunomodulation, Immunomodulating agent, Tinosporacordilifolia

Advances in molecular biology have revolutionized 41 depending on the requirement of the situation. 38 "AcquiredImmunoDeficiency Syndrome" (AIDS).

40 suppression of the immune responses of the host, 58 stimulation and activation of immune effector cells.

24 immunology and medicine. Initially the use of antibody 42 Alternative medicine is now recognized as an invaluable 25 as therapeutic agents was limited by their purity and 43 resource even by the most intransigent clinicians of 26 heterogeneity. Immunotherapy derives from the 44 advanced countries. Plant extracts have been widely 27 observation from the 19th century, that cancer 45 investigated for their possible immunomodulatory 28 sometimes regressed after acute bacterial infections, that 46 properties, Tinospora cordifolia, an indispensable 29 is, there may be no specific immunostimulant effect. 47 medicinal plant, has been used for the treatment of 30 The rapidly expanding discipline of immunology 48 various diseases and has been recommended for 31 contributes to diagnosis, therapy and prevention of 49 improving the immune system. There is great interest in 32 human diseases in many ways. The role of 50 development of new drugs from traditionally used immunocompetents in prevention of malignancy is 51 medicinal plants like Tinosporacordifolia. Ayurveda 34-currently of great interest in experimental science as 52 refers to Tinospora cordifolia as 'Amruth' or the 'Nectar 35 well as clinical medicine. Interest in the immune 53 of Immortality'. The term 'Amruth' is attributed to this 36 response has been stimulated by the alarming increase 54 drug in recognition of its ability to impartyouthfulness, 37 in a novel epidemic form of immune deficiency, 55 vitality and longevity. Immunomodulation can be 56 determined by the capacity of the compounds to Immunomodulation relates to potentiation or 57 influence the cytokine production, mitogenicity,



Fig 1. Tinospora Cordilifolia (Courtesy: KottakkalAryavaidyashala)

Panchabhai et al done a study "Validation of 60 therapeutic claims of *Tinospora cordifolia*: a review "on 61 2008 [1]. As Tinosporia cordifolia is a plant of high 62 pharmacological potential, day by day new studies are 63 conducted and novel therapeutic activities are revealed. 64 Recently, isolation and characterisation 65 phytoconstituents responsible for the activities are done. 66 So, there is a scope for a new study. Tinosporia 67 cordifolia is a plant of high pharmacological potential, 68 day by day new studies are conducted and novel 69 therapeutic activities are revealed. Recently, isolation 70 and characterisation of phytoconstituents responsible for 71 the activities are done. So there is a scope for a new 72 study. The current survey is aimed to include the 75 "amruth".

DESCRIPTION AND HISTORY

78 of family menispermaceae is a perennial, wild climber, 132 polysaccharide, isolated from the dried stem of 79 succulent, shrub often attaining a great height and 133 T.cordifolia showed polyclonal mitogenicactivity 80 sending down long thread like aerial roots. The bark is 134 against beta cell [4]. It was reported that following oral 81 creamy white and grey, leaves are membranous and 135 treatment of mice with water and ethanol extracts of 82 chordate. Flowers grow during the summer and fruits 136 T.cordifolia stems, there was a significant increase in 83 during the winter. The viscous sap has a yellow colour,137 the total of count leucocytes. The aqueous extract of 84 odourand nauseating bitter [2]. It has been used in 138 T.cordifolia was found to increase phagocytosis in vitro. 85 ayurvedic preparations for the treatment of various 139 The aqueous and ethanolic extract also induced an 86 ailments throughout the centuries. Today the drug and 140 increase in antibody production in vivo. T.cordifolia 87 tincture are used for the treatment of general weakness, 141 extracts treatment cause significant reduction in 88 fever, dyspepsia, 89 syphilis, urinary diseases, 90 hepatitis, skin diseases and anemia. In compound 144 20% on placebo reported decrease in the incidence of 91 formulation Guduchi is clinically used to treat jaundice, 145 various symptoms associated with the disease. All 92 rheumatoid arthritis and diabetes. The root is considered 146 extracts

93 as a powerful emetic and is used for bowel obstruction. 94 T.cordifolia is used as an antidote for snake bite and 95 used in malaria, environmental illness, asthma, upper 96 respiratory tract infection, UTI, general debility and 97 amelioration of symptoms from chemo or radiotherapy.

CHEMISTRY

A variety of constituents have been isolated from 100 T.cordifoliaplant. They belongs to different classes such 101 as alkaloids, diterpenoids, lactones, glycosides, steroids, 102 sesquiterpenoids, phenolic, aliphatic compounds and 103 polysaccharides (Table 1). Leaves of this plant are rich 104 in protein (11.2%), calcium and phosphorus [3]. 105 Anarabinogalactan had been isolated from the dried 106 stem of T.cordifolia [4].

PHARMACOLOGICAL ACTIONS

108 Immunological effects

T.cordifolia benefits the immune system in variety of ways. The alcoholic and aqueous extract of this plant 11 have been tested successfully for immunomodulatory 12 activity [5]. Pretreatment with T.cordifolia lead to protection against mortality induced by intra-abdominal sepsis following caecal ligation in rats. It also significantly reduced mortality from E. coli induced peritonitis in mice [6]. In a clinical study, it was afforded protection in cholestatic patients against E. coli sinfection. Those activities were not due to its antibacterial activity as shown by the negative in vitro antibacterial activity of the plant extract. It was reported that treatment in rats had resulted in significant 22 leucocytosis and predominant neutropenia. It has been 23 also observed that it stimulated the macrophages as 24 evidenced by an increase in the number and percentage 73 updated informations available with special emphasis 125 phagocytosis of *S. aureaus* by peritoneal macrophages in 74 on immunomodulatory activity, as its name suggests 126 rats. The phagocytic and intercellular killing capacity of 127 polymorphs in rats, tested at 3.5 hours after E. coli were 128 infection significant. Syringin, Cordiol. 129 Cordioside, Cordifoliosides A&B were identified as the 130 active principle responsible for the anticompliment and T.cordifolia (Fig 1); common name guduchi, amrita 131 immunomodulatory activities [6]. Anarabinogalactan dysentery,gonorrhea,secondary142 eosinophil count and improved hemoglobin in HIV impotency, gout, viral 143 patients [5]. Sixty percent patients receiving TCE and inhibited cyclophosphamide-induced

Types of chemicals	Active principle	Parts in which present
Alkaloids	Berberine	
	Palmatine	
	Magnoflorine	
	Tinosporine	Stem Root
	Choline	
	Isocolumbin	
	Tetrahydropalmatine	
	Magnoflorine	
Glycosides	Tinocordiside	Stem
	Cordiside	
	Syringin	
	Cordifolioside A	
	Cordifolioside B	
	Cordifolioside C	
	Cordifolioside D	
	Cordifolioside E	
	Palmatoside C	
	Palmatoside P	
Steroids	Beta-sitosterol	Aerial part Stem
	gama-sitosterol	
	20B-ecdysone	
	Ecdysone	
	Ecdysterone	
	Makisterone A	
	Giloinsterol	
Diterpenoid lactones	Furanolactone	Whole plant
	Celondane derivatives	
	Tinosporon	
	Tinosporides	
	Jateorine	
	Columbin	
Sesquiterenoid	Tincordifolin	Stem
Aliphatic	Octacosanol	W/l114
Compounds	Heptacosanol	Whole plant
Miscellaneous Compounds	Tinosporidine	Root
	Cordifol	
	Cordifelone	
	Cordifelone	
	Gilonin	
	Tinosporic acid	

147 immunosuppression [7]. The polysaccharide-enriched 164 T.cordifolia treatment, significantly caused the 148 fraction from this plant is found to be very effective in 165 reduction in cell count (p < 0.05) on day 15 of the 149 reducing the metastatic potential of B16f-10 melanoma166 treatment period, however, reduction in total bacterial 150 cells [8]. 167 count was observed from day 3 onwards. The the 168 phagocytic activity and lysosomal enzyme content of (2012)evaluated al. 152 immunomodulatory activity of three polysaccharide-169 milk polymorphonuclear cells enhanced in the diseased 153 enriched immunomodulatory fractions from Tinospora170 cows treated with the T.cordifolia extract. The IL-8 154 cordifolia using the polymorphonuclear leukocyte 171 level in milk serum also increased significantly (p < 1) 155 function test. The results confirmed the 172 0.05) in diseased cows treated with the extract. The 155 immunomodulatory activity of the polysaccharides of 173 results suggest that the hydro-methanolic extract of 157 T.cordifolia, and also it was conclude that the 174 T.cordifolia (stem) possesses antibacterial and 158 polysaccharide with lowest sugar content showed 175 immuno modulatory properties [10]. 159 highest activity and with highest sugar content showed 176 Sharma et al (2012) isolated and characterised the 160 lowest activity [9]. Mukherjee et al evaluate the 177 immunomodulatory active compounds of Tinospora 161 biological activity of the Tinospora cordifolia extract at 178 cordifolia. It was found that ethyl acetate, water 162 standardized dose against bovine subclinical mastitis.179 fractions and hot water extract exhibited significant

163 Intramammary infusion of hydro-methanolic extract of 180 immunomodulatory activity with an increase in

Immunomodulatory activity of Tinosporacordifolia

181 percentage phagocyctosis. 182 purification of these fraction led to the isolation of 240 supplemented cows in comparison to untreated cows 183 seven immunomodulatory active compounds belonging₂₄₁ although plasma total antioxidant activity was similar 184 to different classes such as N-formylannonain, 11-242 between the two groups. Prepartum plasma 185 hydroxymustakone, 186 cordifolioside A , magnoflorine , tinocordiside ,244 the treated group however there was no significant 187 syringin by nuclear magnetic resonance and mass₂₄₅ change in peripartum plasma total estrogens and PGFM 188 spectrometry . Cordifolioside A and syringin have been 246 levels due to Guduchi supplementation [16]. 189 reported to possess immunomodulatory activity. Other 190 five compounds showed significant enhancement in 247 Antidiabetic effects 191 phagocytic activity and increase in nitric oxide and 192 reactive oxygen species generation at concentration 0.1-249 Indian Ayurvedic Medicine for the treatment of 193 2.5 μg/ml [11].

Recently, the presence of an immunomodulatory 195 protein (ImP) in guduchi has been investigated. Guduchi 196 ImP showed ~3-fold mitogenic activity compared to 197 untreated murine splenocytes in the 1-10 μg/mL² 198 concentration range; 5-7-fold increase in mitogenic 199 activity was seen in the case of murine thymocytes vs. 200 control. The purified protein also induced nitric oxide 201 production from macrophages present in isolated 202 murine peritoneal exudates cells. Guduchi ImP displays 203 enhanced phagocytosis of yeast cells by macrophages. 204 Guduchi ImP does not possess haemagglutination 205 activity indicating that the immunomodulatory protein 206 is not a lectin. The confirmation of 207 immunomodulatory protein in guduchi stem showing 208 lymphoproliferative macrophage-activating and 209 properties reinforces the rationale of the use of guduchi 210 preparations for immunomodulation [12].

Cordifolide A, a novel unprecedented sulfur-212 containing clerodane diterpene glycoside, together with 213 other two new diterpene glycosides, cordifolides B and 214C, and four known analogues, were isolated from a 215 methanol-soluble extract of the stems of Tinospora 216 cordifolia. The structures of the new compounds were 217 determined on the basis of spectroscopic data 218 interpretation, with that of cordifolide A confirmed by a 219 single-crystal X-ray crystallographic analysis. All 220 isolates were evaluated for their in 221 immunomodulatory activity using mouse bone marrow-222 derived dentritic cells [13]. Tinosporia cordilifolia had 223 shown a significant level of macrophages activation 224 leads to increase in GM-CSF which leads to 225 leucocytosis and improved neutrophil function [14]. G1-2264A, an immunomodulatory polysaccharide from 227 Tinospora cordifolia, modulates macrophage responses 228 and protects mice against lipopolysaccharide induced 229 endotoxic shock and G1-4A appeared to induce 230 tolerance against endotoxic shock by modulation of 287 berberine down-regulates the high level of free fatty 231 cytokines and nitric oxide [15].

the reproductive performance of crossbred cows by its 290 might play a pivotal role in the treatment of type 2 234 peripartum supplementation, as the crossbred₂₉₁ diabetes [29]. Berberine has been shown to boost the 235 periparturient cow is highly susceptible to various₂₉₂ effects of metformin and 2,4 -thiazolidinedione (THZ), 236 diseases that effectively reduce its reproductive293 and can partly replace the commercial drugs, which 237 performance postpartum. A higher total leukocyte,294 could lead to a reduction in toxicity and side effects of

Chromatographic239 neutrophil lymphocyte ratio was recorded in Guduchi N-methyl-2-pyrrolidone, 243 progesterone concentration was significantly lowered in

The stem of T.cordifolia has long been used in 250 Diabetic mellitus. Oral administration of aqueous T.cordifolia root extract to alloxan-induced diabetic rats caused a significant reduction in blood glucose level and brain lipids [17]. Though the aqueous extract at adose of 400 mg/kg could elicit significant hypoglycemic effect in different animal model, its effect was equivalent to only one unit /kg of insulin [18]. It was reported that the daily administration of either aqueous or alcoholic extract of T. cordifoliadecreases the blood glucose level and increases glucose tolerance in rodents [19, 20]

Berberine, an alkaloid obtained from the stem of T. cordifolia has been tested and used successfully in experimental and human diabetes mellitus. Berberine has been shown to lower elevated blood glucose as effectively as metformin [21]. The mechanisms of action include inhibition of aldose reductase [22], inducing glycolysis [23], preventing insulin resistance through increasing insulin receptor expression [24], and acting like incretins [25]. Berberine also overcome insulin resistance via modulating key molecules in insulin signaling pathway, leading to increased glucose uptake in insulin-resistant cells [26]. Berberine might exert its insulinotropic effect in isolated rat islets by upregulating the expression of hepatocyte nuclear factor 4 alpha, which probably acts solely or together with other HNFs to modulate glucokinase activity, rendering β cells more sensitive to glucose fluctuation and to respond more effectively to glucose challenge [27]. Berberine also seems to inhibit human dipeptidyl peptidase-4 (DPP IV), as well as the pro-diabetic target human protein tyrosine phosphatase 1B (h-PTP 1B), which explain at least some of its anti-hyperglycemic activities. Berberine suppresses intestinal disaccharides 4 with beneficial metabolic effects in diabetic states [28].

A recent comprehensive metabolomics method. 86 applied to type 2 diabetics, suggested administration of 288 acids which are known to be toxic to the pancreas and T.C. was evaluated for the possibility of enhancing 289 cause insulin resistance. These results suggest berberine 238 lymphocyte, neutrophil count along with increased295 the latter. Berberine inhibits Foxo1, which integrates

296 insulin signaling with mitochondrial function. Inhibition350 (ALTC) [35]. Intra-peritoneal administration of ALTC 297 of Foxol can improve hepatic metabolism during 351 in DL-bearing mice not only augment the basic function 298 insulin resistance and the metabolic syndrome [30].

299 Diabetic retinopathy

301 management of diabetic retinopathy due to its356 the tumor growth and increase the life span of tumor 302 antihyperglycemic, anti-angiogenic, anti-inflammatory357 bearing host, thus showing its anti-tumor effect through 303 and anti-oxidant properties. It also prevents the 358 destabilizing the membrane integrity of DL cells. 304 progression of cataract and vascular changes, the 359 T.cordifolia was shown effective in several other 305 important symptoms of DR. Although diabetic rats360 tumour models including Ehrlich ascites carcinoma 306 treated with TC do not achieve the status of normal non-361 (EAC) in mice [36]. It induces proliferation and myeloid 307 diabetic rats, but they achieve significant levels as 362 differentiation of bone marrow precursor cells in a 308 compared to untreated diabetic rats. T. cordifolia thus 363 tumor-bearing host [37], activates tumor-associated 309 acts as a potential therapeutic agent for prevention of 364 macrophages-derived dendritic cells [38], is effective 310 the vascular complications of diabetes.

311 Diabetic neuropathy

Tinospora cordifolia prevents the hyperalgesia in_ 313 expiremental diabetic neuropathy. It has an aldose 314 reductase inhibitory activity in vitro which may 369 315 contribute to the beneficial effects [31].

316 Diabetic foot ulcer

318 an adjuvant therapy showed significantly better final 374 induced 322 immunomodulation for ulcer healing [32].

323 Hypolipidemic effects

325 and as T.cordifolia been shown to have hypoglycemic 322 found in children with moderate degree of behaviour 326 properties, the plant was evaluated for its 383 disorders and mental deficit, along with improvement in 327 hypolipidemicactivity. An aqueous 328 T.cordifolia root was administered to alloxan induced 385 traditionally for its anti-stress activity. The pure 329 diabetic rat (2.5 and 5g/kg body weight for 6 weeks)386 aqueous extract of the root was found to enhance verbal 330 and it reduced serum and tissue cholesterol, 387 learning and logical memory. Both the alcoholic and 331 phospholipids, and fatty acid levels. In another study in 388 aqueous extracts of T.cordifolia produced a decrease in 332 rats, the aqueous extracts also reduced levels of brain 389 learning scores in Hebb William maze and retention 333 lipids [33].

334 Antineoplastic effects

Jagetia et al. have found that the guduchi killed the 336 HeLa cells very effectively in vitro. In this study, the 393 337 stem extracts were evaluated in vitro for their cell394 cisplatin on gastric emptying, but also normalized 338 killing effects [34]. When HeLa cells were exposed to 395 cisplatin-induced hypermotility. The plant was also 339 various doses of the extract, a dose-dependent increase396 found to normalize the phagocytic function of peritoneal 340 in cell killing was observed as compared with non drug-397 macrophages after exposure of rats to either carbon 341 treated controls. The methylene chloride extract was the 398 tetrachloride or serum, thus it satisfied the definition of 342 most potent. The effect of guduchi extract was 399 adaptogen [42]. 343 comparable or better than doxorubicin treatment and 400 Antioxidant activity 344 thus it indicates that the plant warrants a future study as 345 anti-neoplastic agent. Further investigation were 401 346 undertaken to study whether the tumor associated 402 were studied by administering the aqueous extract of 347 macrophages (TAM)of Daltons lymphoma (DL) a403 alloxan-induced diabetic rats. After 6 weeks, the level 348 spontaneous transplantable T-cell lymphoma, can be404 of plasma barbituric acid reactive substances,

352 of macrophages such as phagocytosis as well as their 353 antigen-presenting ability and secretion of IL-1 and 354 TNF. The results of the investigation also indicate that T. cordifolia plays role in prevention and 355 the intra-peritoneal administration of ALTC slow down 365 against various cancers, killing the cancer cells very 366 effectively in vitro, inhibits skin carcinogenesis in mice 367 [39], and inhibits experimental metastasis [8].

68 Cognitive effects

The memory impairment induced by cyclosporine 370 was successfully overcome by both the alcoholic and 371 aqueous extract of T. cordifolia. 372 histopathologically, T.cordifolia has successfully Diabetic patients with foot ulcers on T. cordifolia as373 reversed the hippocampal neuronal degeneration cyclosporine revealed by 319 outcome with improvement in wound healing. Reduced 375 histopatholagical investigation [40]. The alteration of 320 debridements and improved phagocytosis were 376 immune function affected learning and memory process 321 statistically significant, indicating beneficial effects of 377 and T. cordifolia is a potent immunomodulator and 378 cognitive enhancer. The dual property of T. cordifolia 379 may bear a potential use in neurodegenerative disease 380 affecting cerebral neurons and immunosuppression Diabetics are often associated with hyperlipidemia 381 induced memory changes. Significant response has been extract of 384 IQ levels. The root of *T.cordifolia* is is known to be used 390 memory, indicating enhancement of learning and 391 memory [41].

392 Adaptogenic effects

The aqueous extract not only reversed the effect of

The antioxidant properties of *T. cordifolia* roots 349 activated by the aqueos liquid extract of T.cordifolia405 ceruloplasmin and alpha tocopherol were reduced. In

Immunomodulatory activity of Tinosporacordifolia

407 increased. The root extract at a dose of 5 g/kg was the 464 subacute inflammation, the drug was inferior to 408 most effective one [43]. In another study, guduchi465 phenylbutazone [48]. The aqueous extract of stem was 409 extract was shown to inhibit the lipid peroxidation 466 reported to exert a significant anti-inflammatory effect 410 superoxide and hydroxyl radical in vitro. Earlier studies467 in both cotton pellet-induced granuloma (1, 250 and 411 shows that dry stem crude extract (DSCE) contains a468 500 mg/kg given orally) and formalin-induced arthritis 412 polygonal beta cell mitogen; G1-4A, DSCE as well as469 (1 mg/kg given orally) rat models. 413 G1-4A also enhance immune response in mice [44]. In 414 order to explore the possibility of using G1-4A/pp1 to 415 modulate radiation-induced immune suppression, the 471 416 antioxidant effect PPI from of this plant was examined 472 the experiment in which goats treated with T.cordifolia 417 against reactive oxygen and nitrogen species473 have shown significant clinical and hematobiological 418 (ROS/RNS), generated 419 photosensitization/peroxynitrite. Oxidative 420 induced by peroxynitrite was inhibited by PPI. The 476 inactivating property against hepatitis B and E surface 421 degradation of protein due to photosensitization477 antigen in 48-72 hours [50]. Oral administration of 422 assessed by SDS PAGE was effectively reduced by 478 Tinospora cordifolia stem and leaves extract prevented PPI 423 simultaneous treatment with 424 photosensitization. Selective inhibitors of ROS-like480 Swiss Albino mice [51]. T. cordifolia exhibited time-425 mannitol, super oxide dismutase (SOD), Sodiumazide, 481 dependent hepatoprotection as reflected in both 426 ant-oxidant GSH, and vitamin C brought about 482 biochemical and histological examination in a study 427 significant inhibition of formation of TBARS thus483 conducted in Albino Wistar rats against CCl4-induced 428 indicating generation of oxygen. Thus the action of PPI484 hepatic damage. Extract effectively control the ALT, 429 may be against oxidative damage through type 1 and 485 ALP 430 type 2 photosensitization mechanism. T. cordifolia486 histopathological studies proved the hepatoprotective 431 has also been reported to elevate GSH levels, expression 487 activity of extract [52]. 432 of the gamma-glutamylcysteine ligase and Cu-Zn SOD 433 genes. The herb also exhibited strong free radical-434 scavenging properties against reactive oxygen and 489 435 nitrogen species as studied by electron paramagnetic490 serum and heart lipid peroxide levels was observed with 436 resonance spectroscopy [45].

437 Anti-inflammatory, anti-arthritic and anti-438 osteoporotic activities

It is traditionally used in compound formulations for 495 streptozotocin-induced diabetic 440 the treatment of rheumatoid arthritis. The alcoholic496 benefiting the heart [54]. Administration of the extract 441 extract of T. cordifolia has been found to exert anti-497 of T. cordifoliaroots (2.5 and 5.0 g/kg body weight) for 442 inflammatory actions in models of acute and sub4986 weeks resulted in a significant reduction in serum and 443 acuteinflammation [46]. The water extract of the stem of 499 tissue cholesterol, phospholipids and free fatty acids in 444 neem-giloe cordifolia that grow 445 Azadirachtaindica (neem)] significantly inhibited acute 501 Osteoprotective activity 446 inflammatory response evoked by carrageen in a dose of 447 50 mg/100 g given orally and intraperitoneally. A⁵⁰² 448 significant inhibition of primary and secondary phases503 weight) showed an osteoprotective effect, as the bone 449 of inflammation was observed in a model of adjuvant-504 loss in tibia was slower than that in controls. Serum 450 induced arthritis. It also significantly inhibited antibody505 osteocalcin and cross-laps levels were significantly 451 formation by typhoid "H" antigen. A mild analgesic506 reduced. This study demonstrates that extract of T. 452 effect of its own as well as potentiation of morphine 507 cordifolia has the potential for being used as 453 analgesia has been reported [47]. In another study508 antiosteoporotic agent [56]. 45 aqueous extract of T. cordifolia showed a significant 455 inflammatory effect in the cotton pellet granuloma and 509 Anti-allergic activity 456 formalin induced arthritis model, its effect was 510 comparable with indomethacin and its mode of action511 asthma, and the juice is also employed for the treatment 458 appeared to resemble that of non-steroidal anti-512 of chronic coughs [57]. In a clinical study, 100% relief 459 inflammatory agent. The dried stem of T. cordifolia513 was reported from sneezing in 83% of the patients on 460 produced significant anti-inflammatory effect in both514 treatment with T. cordifolia. Similarly, the relief from 461 acute and subacute models of inflammation. T.515 nasal discharge was reported in 69%; from nasal

406 addition, the level of glutathione and vitamin C were 463 acetylsalicylic acid in acute inflammation, although in

70 Hepatoprotective effects

The hepatoprotective action was reported in one of by 474 improvement in CCL₄-induced hepatopathy [49]. damage475 Extract of T.cordifolia has also exhibited in vitro during479 the occurrence of lead nitrate induced liver damage in and total bilirubin levels

88 Cardioprotective activity

A dose-dependent reduction in infarct size and in 491 prior treatment with *T.cordifolia* in ischemiareperfusion-induced myocardial infarction in rats [53]. 493 The stem extract can normalize the alterations in lipid 494 metabolism caused by diabetes mellitus in rats, on 500 alloxan-induced diabetic rats [55].

Rats treated with T. cordifolia (10 mg/kg body

T. cordifolia is traditionally used for the treatment of 462 cordifolia was found to be more effective than 516 obstructions 61% and from nasal pruritis, in 71%. In

517 placebo group, there was relief from sneezing only in 573 gluconeogenic enzymes activity in diabetic rat kidney 518 21% patients; from nasal discharge, in 16.2%; from 574 [66]. The ethanol extracts of the roots of T. cordifolia 519 nasal obstruction, in 17%; and from nasal pruritis, in 575 Miers and C. asiatica Linn were observed to induce a 520 12%. Thus, T. cordifolia significantly decreased all576 marked protective action against an 8 h restraint stress 521 symptoms of allergic rhinitis and was well tolerated 577 induced ulcerization, the activity being comparable to 522 [58]. The anti-allergic and bronchodilator properties of 578 that of diazepam [67]. Concurrent daily administration 523 an aqueous extract of the stem evaluated on histamine-579 of T. cordifolia stem and leaves extract prevented the 524 induced bronchospasm in guinea pigs, capillary580 toxic influences of lead on haematological value and the 525 permeability in mice and mast cell disruption in rats581 results suggested that simultaneous supplementation of 526 showed that it significantly decreased bronchospasm582 T. cordifolia protects against lead intoxication [68]. 527 induced by 5% histamine aerosol, decreased capillary 528 permeability and reduced the number of disrupted mast583 Clinical uses 529 cells.

530 Antipyretic and anti-infective activity

The water-soluble fraction of 95% ethanolic extract 532 of T. cordifolia plant has shown significant antipyretic 533 activity [59]. In another experimental study, antipyretic 534 effects have been reported in the hexane- and 535 chloroform-soluble portions of *T. cordifolia* stems [60]. 536 Various studies show remarkable anti-infective and 537 antipyretic properties of *T. cordifolia*. Pre-treatment 538 with T. cordifolia was shown to impart protection 539 against mortality induced by intra-abdominal sepsis 540 following caecal ligation in rats and significantly 541 reduced mortality from induced by E. coli-induced 542 peritonitis in mice [61].

543 Antifertility & aphroadisiac activity

545 cordifolia stem to male rats at a dose level of 100 mg/d600 It has no side effect and toxicity. When T. cordifolia 546 for 60 days did not cause body weight loss but601 extract was administered to rabbit up to the highest oral 547 decreased the weight of testes, epididymis, seminal 602 doses of 1.6 g/kg, there were no predictable adverse 548 vesicle and ventral prostate in a significant manner [62].603 drug effects. 549 Gudichi is a natural aphrodisiac in females. Its 550 immunomodulatory action helps to strengthen the 551 immune system and to make the body stronger and 604 552 hence make a woman more able and ready to enjoy the 605

554 Other effects

In a clinical evaluation, a compound preparation 609 potential in modern pharmacotherapeutics. 556 'RUMALAYA' containing T.cordifolia was reported to 557 significantly reduce the pain in patient suffering from 558 rheumatoid arthritis. Ether extract of the steam distillate 559 of aerial part of *T.cordifolia* has inhibited the *in vitro* 560 growth of Mycobacterium tuberculosis at 1:50,000₆₁₃ 561 dilutions [63]. It is used for its anti-leprotic properties, 6142. 562 along with wide use in other types of skin disorders and 615 563 has been shown to exert antileprotic activity in a616 564 combination formulation. Ethanolic extract of 6173. 565 T.cordifolia has exhibited significant antipyretic activity 618 566 in rats [64]. 'Septilin syrup ' a compound preparation 619 4. 567 containing *T.cordifolia* was found to elicit good clinical⁶²⁰ 568 response in children suffering from upper respiratory 621 569 tract infection and chronic otitis media. In a scientific 570 study on rats and human volunteers, T. cordifolia was 571 found to have diuretic effects [65]. It was also found 625 572 effective in modulation of morphology and some626

T. cordifolia is used clinically in the Indian system 585 of medicine for the treatment of jaundice, diabetes and 586 rheumatoid arthritis. It has also been found to posses adaptogenic, antinflamatory, anti-neoplastic, antioxidant, hepatoprotective, cognitive, hypolipidemic, antimalarial, antistress, antipyretic and immunologic properties. There are limited human studies to support these use. T. cordifolia can also be used as an adjuvant drug in the treatment of hyper-reactive malarious splenomegaly [69]. Tinospora cordifolia appears to improve surgical outcome by strengthening host defenses as evidenced by the study on surgical outcome in patients with malignant obstructive jaundice [70].

597 Toxicology

The ayurvedic literature reports that T. cordifolia Oral administration of 70% methanolic extract of T. 99 can cause constipation, if taken regularly in high doses.

CONCLUSION

The pharmacological actions attributed 553 sex. It is a rejuvenator and a natural herbal aphrodisiac. 606 T.cordifolia in ayurvedic texts and folk medicine have 607 been validated by a remarkable body of modern 608 evidence suggesting that this drug has immense

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