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ROLE OF *TINOSPORA CORDIFOLIA* (GILOY) IN BONE MAINTENANCE DISORDER (OSTEOPOROSIS) BY DOCKING ANALYTICAL STUDY

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ABSTRACT

T. cordifolia commonly known as guduchi is an indigenous plant and has medicinal values for ethnic groups of Himalayan region. It belongs to the family Menispermaceae. It is traditionally valued for rejuvenile drug with immune-modulatory potential, treatment of gout, meha, antidote of snake bite. This review paper provides comprehensive information on the botany, traditional uses, phytochemistry, and pharmacological research on *T. cordifolia*, based on the scientific literature. It has important role in local and popular medicine, specifically for boosting immune system in humans and helps to improve bone related disorder like, Osteoporosis (Fig 1). More than 30 active constituents are present in this plant that can be extracted by ethanolic extraction process. They are highly active to bind with RANKL/ OPG genes. This in-silico docking study suggest Berberine, Palmatine, cordifolioside A, Tinosporinone, Ecdysterone, Isocolumbin and Tinocordifolin have low binding affinity and they carry significant role in Bone maintenance disorder (Osteoporosis).

KEY WORDS- *T. cordifolia,* Guduchi, Osteoporosis, Osteoblast, Osteoclast, RANKL, OPG, BMD, M-CSF.

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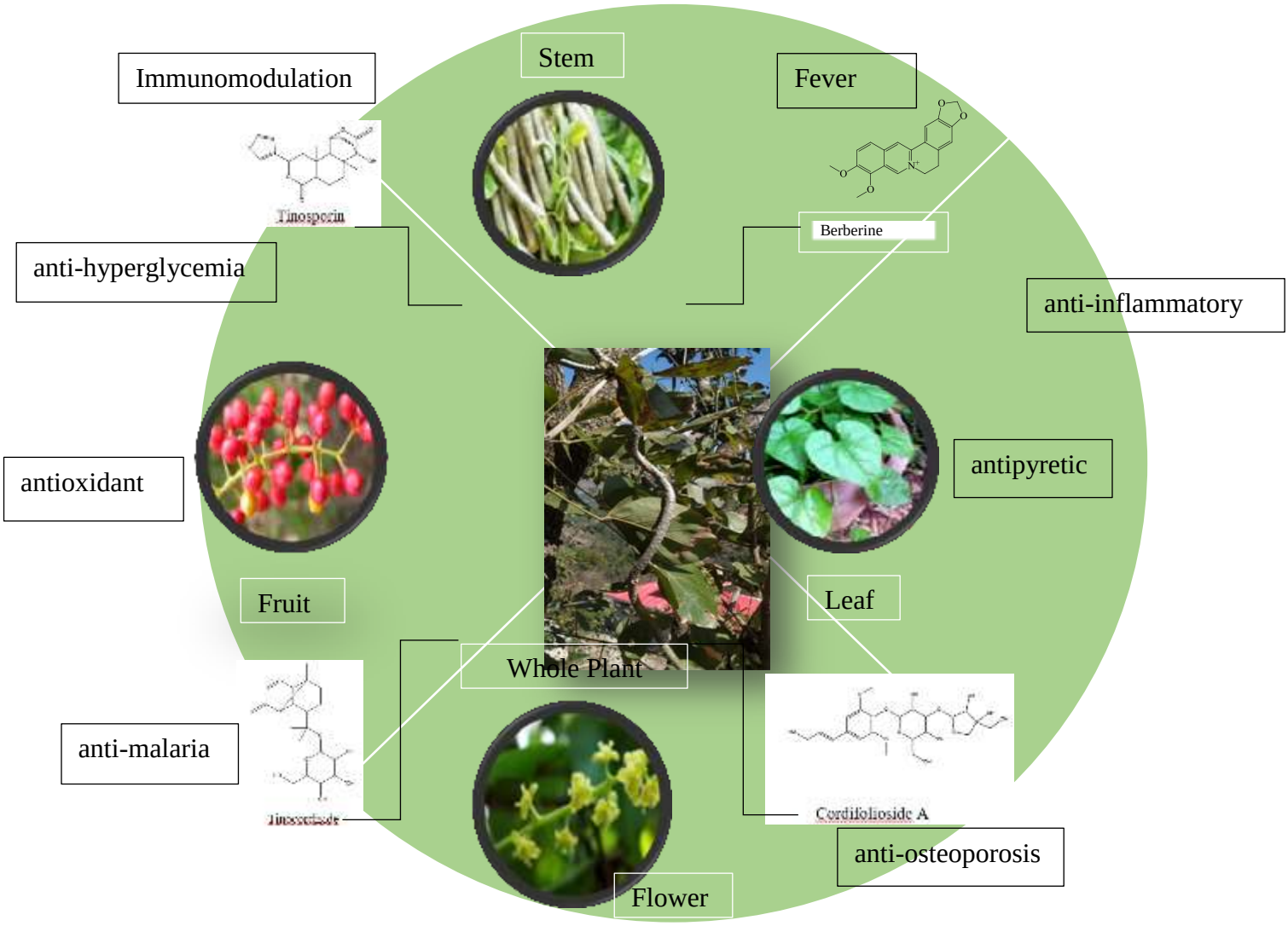

Fig 1- T. cordifolia is used traditionally to cure several disease

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1. INTRODUCTION

T. cordifolia, climbing shrub used in the treatment of uncountable diseases such as diabetes, rheumatoid arthritis, gonorrhea, secondary syphilis, anemia, dermatological diseases, cancer, gout, jaundice, asthma, leprosy, bone fractures, liver & intestinal disorders, purifies the blood. It native to India (Fig 2), Sri Lanka, Myanmar, China, Bangladesh, South Africa and West Africa. Some of the drugs are trusted to encourage positive health and maintain resistance against infections. It is one of the main genera of Menispermaceae family. The family consists of approximately 70 genera with 450 species that find in tropical regions (Choudhary, et al., 2013). There are about 34 species of *Tinospora* distributed worldwide such as, *T. cordifolia, T. capillipes, T. capillipes, T. sagittata, T. sinensis, T. oblongifolia, T. hainanensis*, etc. *Tinospora* genus increase immune system, prevent respiratory infections, also treat for diabetes (Chi, et al., 2016). There are more than 100 vernacular names of this plant like, seendal, chittamruthu, amrita, amrutha balli, etc. This plant commonly known as 'Guduchi' in Sanskrit, 'Giloe' in Hindi and 'Heart-leaved Moonseed plant' in English. In Ayurveda *Rasayana*, the plant is commonly known as "Amrita" and have an adaptogen and anti-stress activity (Bharath, et al., 2020). From ancient time some Ayurvedic medicines are prepared from this plant such as, *Sanjivanivati, Amritashtakachurana, Kanta-kariavleha, Dashmoolarishta, Guduchisaatva, Guduchighrita,* etc. (Sharma, et al., 2018).

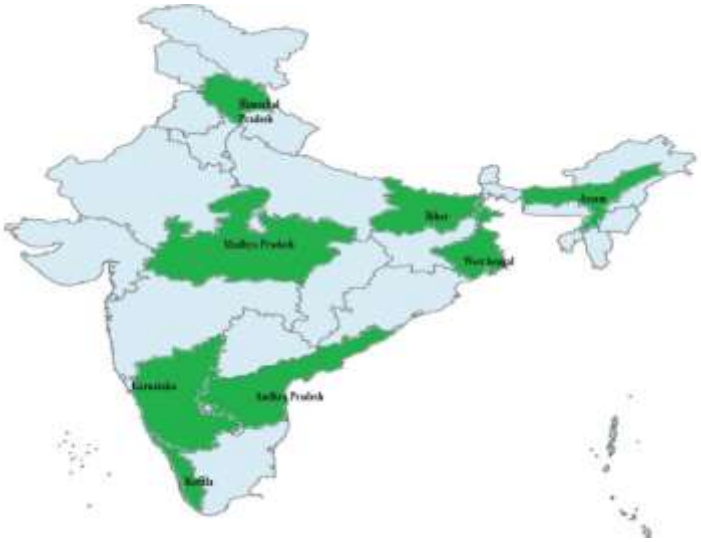

Fig 2- Geographical distribution of *T. cordifolia* in India

Osteoporosis, a major skeletal disease that affects both men and women, causes mainly estrogen deficiency, reduction in bone mineral density and bone deterioration. According to statistics from the International Osteoporosis Foundation, it has been estimated that more than 200 million men and women are suffering from osteoporosis. Approx. 1in 3 women over 50 years old and 1 in 5 men will osteoprotic (Sarafrazi, et al., 2021).

2. OBJECTIVES

To comprehend the fragmented literature available on the botanical & geographical description, traditional use, phyto-chemistry, pharmacological properties of *T. cordifolia* and detail molecular biology of bone maintenance and disorders consist with gene expressions.

The main aim of this review article is to improve bone re-absorption, cure bone disorder like Osteoporosis by Giloy, *as* it is an plant so it's active constituents have less side effect. The active constituents of this plant have several pharmacological use. All the structure of active constituent present in *T. cordifolia* are given below.

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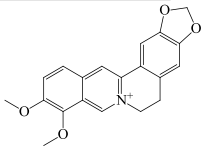
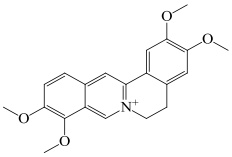
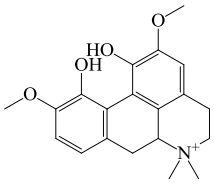
Alkaloids



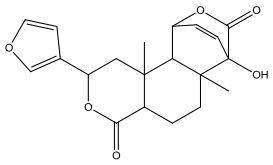
Berberine



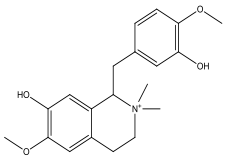
Palmatine



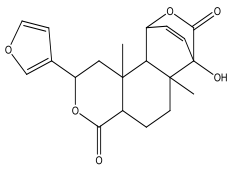
Magnoflorine



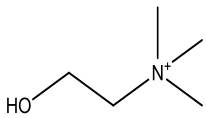
Tinosporin



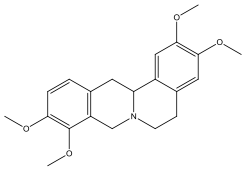
Tembetarine



Isocolumbin

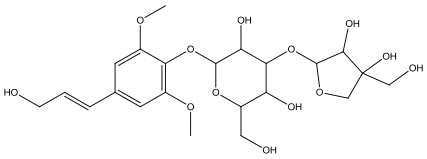


Choline

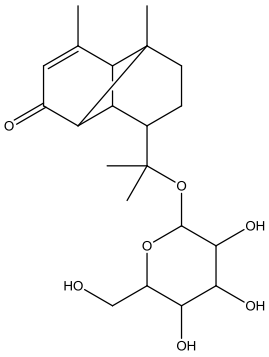


Rotundine

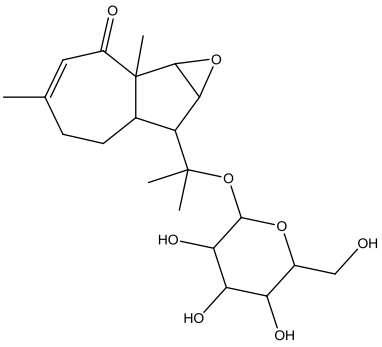
Glycosides



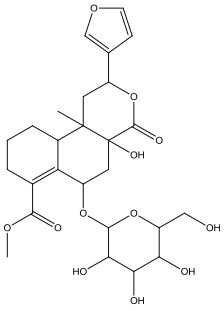
Cordifolioside A



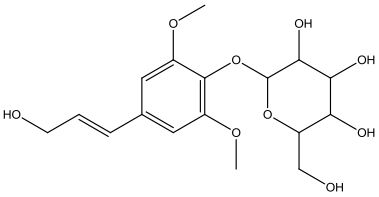
Tinocordiside



Tinocordifolioside



Cordioside



Syringin

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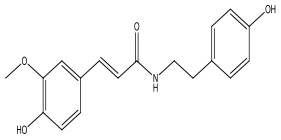
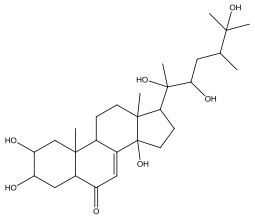
Miscellaneous compounds

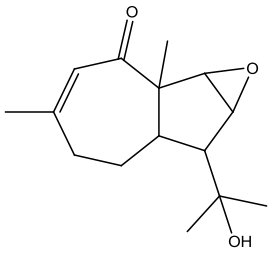


N-trans-Feruloyltyramine



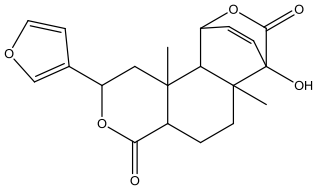
Makisterone A

Sesquiterpinoids

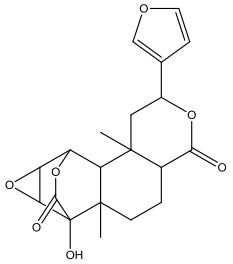


Tinocordifolin

Diterpenoid lactones



Columbin



Tinosporide

Aliphatic compounds

Heptacosanol

Nonacosan-15-one

Octacosanol

2.1. Bone Biology

Bone modeling and remodeling maintain through the balanced of osteoblast and osteoclast, that are responsible for bone resorption and bone formation respectively. For menopausal women the loss of bone mineral density after 5- 10 years of menopause is termed postmenopausal or age-related osteoporosis (Gao, et al., 2021). Estrogen, a strong inhibitor of function and differentiation of osteoclasts. Estrogen deficiency origins the expression of the estrogen-induced receptor activator for nuclear factor kappa- B ligand (RANKL), antagonist osteoprotegerin (OPG) to decrease, resulting in activation and proliferation of osteoclasts through the OPG/ RANKL pathway. The bone re-modelling cycle take place in 5 stages- **Activation,** In which stage osteoblastic expression of M-CSF (macrophage colony-stimulating factor) and RANKL stimulate pre-osteoclast progenitor maturation and diferentiation into osteoclasts). **Re-absorption** of bone by the help of osteoclasts. **Reversal**, formation of new bone by osteoblasts. **Termination**, bone returns to quiescent phase. **Bone re-modelling** is stimulated by PTH and calcitriol, is inhibited during the quiescent phase by sclerostin, which inhibits WNT signaling driven bone development and OPG which inhibits RANK-RANKL interaction (Rowel, et al., 2022) (Fig 3).

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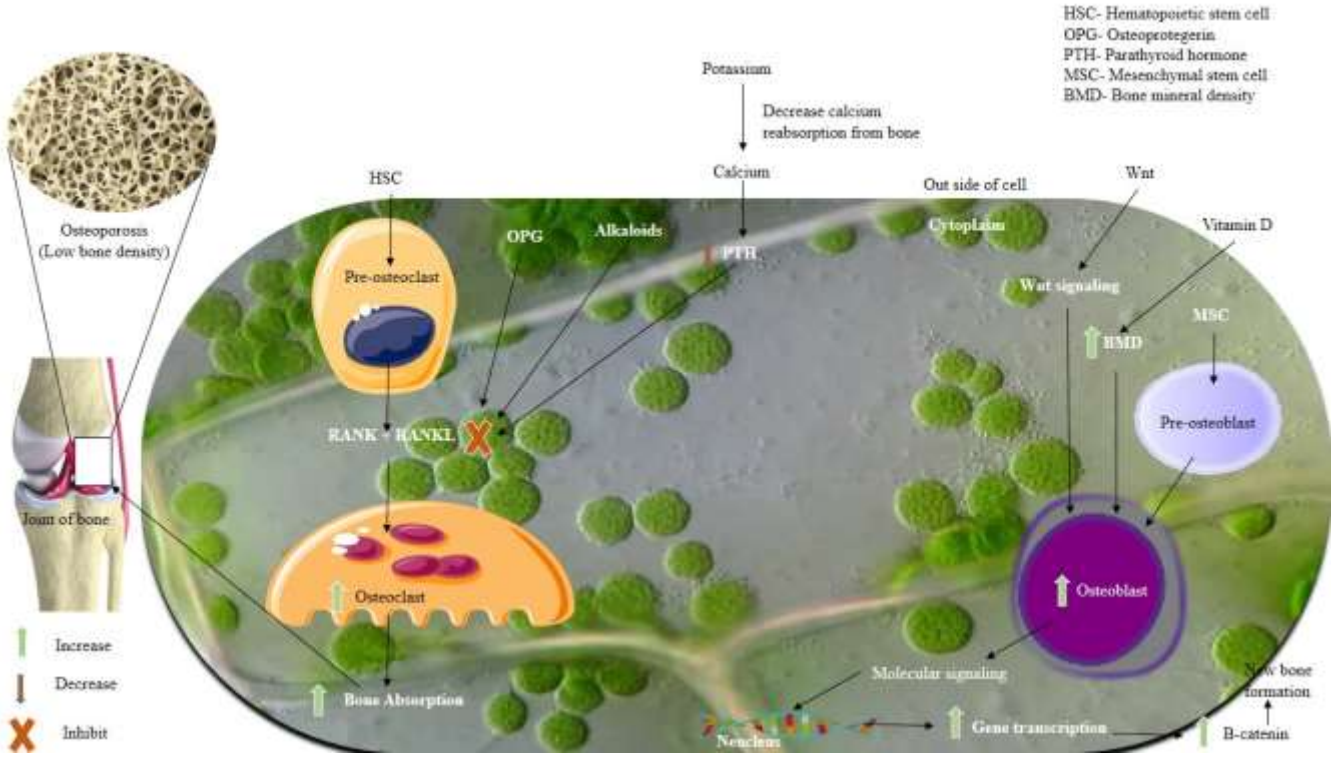

Fig 3- Re-modelling cycle and regulators of bone.

3. TREATMENTS

There are several pharmacological options for osteoporotic treatment that aim to decrease the risk of fractures. These include:

- Calcium and vitamin D
- Antiresorptive therapy- Denosumab, Bisphosphonates (They bind strongly to hydroxyapatite which inhibit osteoclast-mediated bone resorption, increase BMD).
- Hormonal treatment- PTH analogues, Testosterone, Selective oestrogen receptor modulators (They decrease the RANK-RANKL interaction for that osteoclast activity decrease).
- Novel therapies- Romosozumab, Dickkopf-1 (Dkk1) inhibitors (They work as an antagonist of Wnt molecular signaling pathways, increase osteoblastic activity for bone formation) (Barnsley, et al., 2021).

4. RESULTS & DISCUSSION

Molecular docking study of *T. cordifolia* active constitutes and their activity on RANKL/ OPG with tinosporinone (Fig 4)- Tinosporine is an alkaloids with molecular formula $C_{19}H_{18}O_6$, 342.3 molecular weight, containing canonical SMILES- CC(C(=O)C1=CC2=C(C=C1)OCO2)C(=O)C3=C(C=C(C=C3)OC)OC, present in *T. cordifolia*. In chemical compound data base (Pub chem) Tinosporine is known as Tinosporione, Pubchem CID- 42607646. According to molicular docking It is hingly active compond can bind with H bonds, Z chains of RANKL/ OPG. In figure 5 we can see the green area becomes less after binding as Tinosporione rstrick the Z chain and H bonds of the RANKL/ OPG (Table 1).

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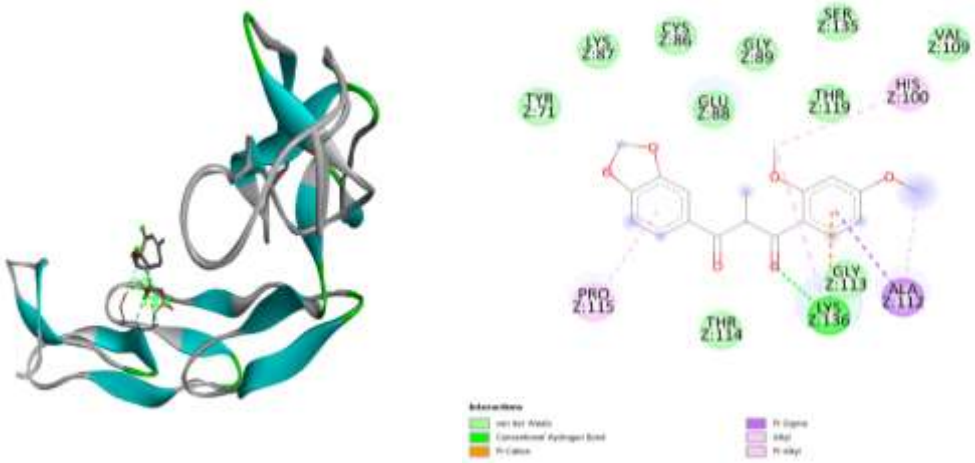
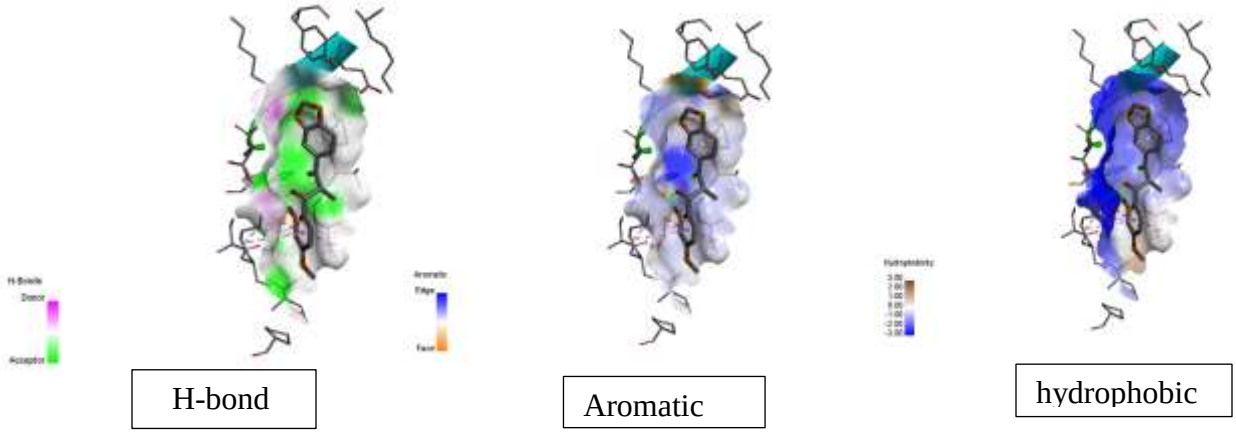


Fig 4- Tinosporinone binding to z-chain of RANKL/OPG complex



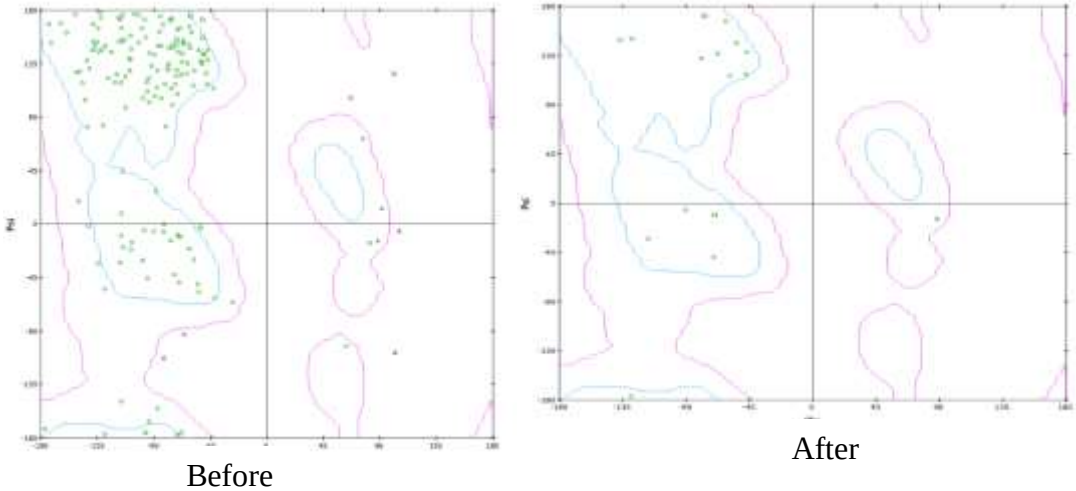


Fig 5- Ramachandrandran plot for z-chain of RANKL/OPG before and after docking with tinosporinone.

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Table 1- Binding Affinity of different ligands on RANKL/OPG complex		
Sl. No.	**Ligand- RANKL/OPG complex**	**Binding Affinity**
1.	Tinosporinone (3urf.mod_100926540_uff_E=1853.03)	-5.2
2.	Berberine (3urf.mod_2353_uff_E=579.86)	-6
3.	Ecdysterone(S) (3urf.mod_12304165_uff_E=1002.21)	-5.9
4.	Isocolumbin (3urf.mod_24721165_uff_E=902.37)	-6.4
5.	Tinocordifolin (3urf.mod_100926540_uff_E=1853.03)	-5.2

5. CONCLUSION

As a versatile traditional medicine, *T. cordifolia* is a promising ethno-medicinal plant with extracts and phyto compounds exhibiting multifarious bioactivities. The extensive literature survey revealed, Giloy used for the treatment of antibacterial, antioxidant, and anti-inflammatory, anti- cancer, antioxidant, antiulcer, antidiarrheal, neuroprotective, gastroprotective, hepatoprotective and antidepressant from ancient time. Traditional uses of Giloy has validated through in vitro and in vivo pharmacological studies. Present review focussed on the Molecular docking on RANKL/ OPG gene, which play an important role in Bone maintenance disorder. Currently, more than 41 compounds have been isolated by ethanolic extraction process; among them Berberine, Palmatine, cordifolioside A, Tinosporinone, Ecdysterone, Isocolumbin, Tinocordifolin are the major active constituents. In-depth studies on chemical ingredients, their natural activity site, binding affinity to the RANKL/ OPG genes are needed to be conducted with some clinical practices on rats. Moreover, clinical trials are needed to identify any adverse effects and possible interactions between this herbal drugs and synthetic medicines containing Berberine, Palmatine, cordifolioside A, Tinosporinone, Ecdysterone, Isocolumbin and Tinocordifolin. Several studies suggest that this plant is non-toxic, meaning that the dose needed for showing pharmacological activities are very low compared to their toxic levels. To better establish the safety limits for this plant toxicity studies should be carried out.

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