



### Thyroid: Functional Food (Family Welfare, Family Physician, Nurse, Computational Validation, and Drug Discovery)

Deepak Bhattacharya, PhD<sup>1\*</sup>; Chandra Sekhar Tripathy, M.Sc<sup>2</sup>; Hadi Sajid Abdulabbas, MD<sup>3</sup>; Yasir Haider Al-Mawlah, PhD<sup>4</sup>; Asadollah Asadi, PhD<sup>5</sup>; Arash Abdolmaleki, PhD<sup>6</sup>; Mahtab Pouyanfar, PhD<sup>7</sup>; Muhammad Akram, MD, PhD<sup>8</sup>; Gaurav Giri, BAMS<sup>9</sup>

<sup>1</sup> Social Service & Nursing, Sri Radha Krishna Raas Mandir, Kedar Gouri Road, Bhubaneswar, Odisha, India.

\* Corresponding Author. Email: [fightcancermetastasisathome@gmail.com](mailto:fightcancermetastasisathome@gmail.com)

<sup>2</sup> School of Applied Sciences, Centurion University of Technology and Management (CUTM), Bhubaneswar, Odisha, India.

<sup>3</sup> Lecturer, Continuous Education Department, Faculty of Dentistry, University of Al-Ameed, Karbala, 56001, Iraq.

<sup>4</sup> DNA Research Center, University of Babylon, Babylon, Iraq.

<sup>5</sup> Associate Professor, Department of Biology, University of Mohaghegh Ardabili, Iran.

<sup>6</sup> Assistant Professor, Animal Physiology, Department of Biology, Faculty of Advanced Technologies, University of Mohaghegh Ardabili, Iran.

<sup>7</sup> Instructor, TVTO-Medicinal Plants, Teheran, Iran.

<sup>8</sup> Chairperson, Dept. of Eastern Medicine, Government Medical Collage, Faisalabad, Pakistan.

<sup>9</sup> Asst. Drugs Controller, Dept. of AYUSH, Govt. of Odisha, Bhubaneswar, India.

#### ARTICLE INFO

##### Article History:

Received: June 22, 2023

Accepted: August 1, 2023

#### ABSTRACT

**Background:** Thyroid hormone is related to metabolism, a poly-organ normal function including blood chemistry, hemodynamics and erythropoiesis. Hypertrophic gland causes iodine deficiency and rarely cancer. Hypothalamus signals pituitary gland to produce thyroid-stimulating hormone (TSH), which regulates hormone production. Insufficient TSH uptake and/or inefficient conversion is pathophysiology. Current standard medication for pathophysiology is long-period 'hormone replacement therapy' (HRT) with no prophylaxis, no cure, no synergic medicaments, and no functional foods (FFs). **Purpose:** Reporting a few functional foods and examine its theoretical affinity with safety and discussing (ground breaking) role of nurses. **Methods:** Home - and clinic- based observation of use of FFs (alongside HRT) which are, (a) Star Anise -*Illicium verumtree* (b) Cinnamon bark - *Cinnamon verum/cassia*, and (c) Fruit & flower of *Myristica fragrans* and computational validation of the principal moieties which are, (i) caffeic acid and (ii) Cinnamic acids. **Results:** Clinical & home-based family member's observations confirm an apparent better effect of 'FF' supplementation along with 'feel good factor'. Theoretical-computational interaction is observed between TSH with compounds (i) & (ii); binding affinity being -5 kcal/Mol with a minimum of 4 'H' bonds at ~ 2 Å distance and a stable-high 'inhibition constant' of >180µm. **Conclusion:** Goiter is chronic; treated as out-patient; sporadic approach; and expensive. FFs which are, (a), (b), (c) and compounds (i) & (ii) present with likeness; compatibility with TSH as drug discovery candidates at the molecular level and also as 'synergic' with TSH. 'a-b-c' beholds to the immediate possibility of use as 'functional foods' targeting TSH uptake and/or efficient conversion. Goiter needs case specific nursing interventions. **Implications for Nursing:** Thus far, nursing role is needed for treatment of goiter. Predominantly a female who silently is suffering from Goiter has mood-swings, non-compliant with medication, with work-hour loss. Nurse's assuring voice; close company guidance; In-Silico validated FF use opens wide a new vestibule between goiter care and drug discovery with nurse as the vital connect. Nurse's role is indispensable in bottom-up drug discovery models.

**Keywords:** Thyroid, TSH, Functional food, Caffeic acid, Cinnamic acid, PDB.

### What does this paper add?

1. The role of nurses and swath of nursing is expanding including meteorology cased large scale medical emergencies called ‘medical meteorology’ (Bhattacharya-c 2023). This communication seeks to bring to light that goiter worldwide has no (i) curative therapy and HRT is not curative (ii) no identified and validated functional foods (iii) nursing being at full discount. That is, (a) Star Anise -*Illicium verumtree* (b) Cinnamon bark - *Cinnamon verum/cassia* (c) Fruit & flower of *Myristica fragrans* posit as excellent FFs – first ground breaking work. Also, (i) *caffaic* (ii) Cinnamic acids are safe and have good likeness, compatibility with TSH at molecular level; as ‘synergic’ with HRT and posit as champion ‘starting material’ candidates in drug discovery.
2. Goiter nursing is prominent by absence and needs to be and can be nursed 24 x 7 (clinically at home – tele-nursing). Goiter is associated with acute mood swings, management of which is in eminent need of the assuring-embalming nurse. Nursing of goiter using our candidates and or any natural compounds is conspicuous by absence (Mathew et al., 2023). Nurses’ best points to fruitful ‘bottom-up-model’ in drug discovery and economies-of-scale.

### Introduction

The throat’s architecture adds beauty to the body, is sensuous and an engineering marvel. In the western schools of conventional medicine, any bulge/deformity in such architecture has been termed ‘goiter’ (gullet -gut connector’s malady). Its stemm is traced to Franco-Latino lingual phones and it denotes the thyroid gland. Staring with Leonardo Da Vinci (c.1500 A.D.) naming it as ‘thyroid’ (Greek throat armor of such name, c.5<sup>th</sup> B.C.); gland’s study (vertebrate-endocrine); placement as a vital hormone (thyroxin group) producing sub-organ; finding iodine; pituitary nexus for stimulation and finally ‘hormone replacement as therapy’ (HRT) involves many un-putdownable stories and many immortal names extending to the 20<sup>th</sup> century (Conelly et al., 2022; Niazi et al., 2011). Goiter has not gone (Kotwal et al., 2007; Taylor et al., 2018). Learned labour continues. Present best in brief is that goiter is of (i) simple and non-toxic (ii) nodular and toxic. Mostly, it is non-cancerous due to iodine deficiency or down-turned iodine metabolism, where all types respond well to iodine and ‘hormone replacement therapy’ HRT (Loyal et al., 2017; Szkudlinski et al., 2002).

Primary malignancies are few and far-distant (Olson et al., 2019; WHO, 2014) due to its atypical construction, high vascular drainage, unique bio-physics, neck-nape bio-mechanics and endocrine function (own unpublished data). Malignancies are mostly metastatic (secondary) having nexus with lymph and sub-normal sentinel node signature (own unpublished data). Among the schools of oriental medicines, Sino-Nipponese are noted to have an over-emphasis on acupuncture (Lee et al., 2021) and fixed dose internal medicine is absent (Cidian, 2005; Read, 1936). Thyroid therapeutics in the Persian (Avisenna 11<sup>th</sup> A.D.) and the Indian Islamic region (Siddiqi, 1959) including Middle East, Asia-Minor and Central-Asian schools do not present us with any prescription (in public domain; focused systematic study is very scant). Functional food-based African ethnic/traditional medicaments are noted (Al, 2022; Taibi et al., 2021). The Indian National School; i.e., Ayurveda (plural aging) which pre-dates Hippocrates (Bhattacharya-a, 2009) terms swelled thyroid presentation as ‘galoghontaka/galaganda’ (defective/lumpy-throat) in India’s national techno-lingual phone; i.e., Sanskrit (self-gelling) and lays down ‘n’ number of formulations; pharmaceutical process to make fixed-dose therapeutics comprised of mono-herb or poly-herbs (Bhattacharya-b, 2014). During the last two decades, clinical groups worldwide have tried out many a multi drug therapies, mixopathies with and without HRT for goiter remains. Moreover, due to life-style changes in the developing high census nations and the expansion of diagnostics, goiter numbers are having an exponential jump (FAO, 1980). HRT is galloping too (Cagnacci & Venier, 2019; Cooper & Blair, 2016) and it has dark downsides (Bae, 2021; Bartalena et al., 2019), especially as it involves long-scope intake, ever increasing dose with individual specific systemic response (ideo) pathologies. Also, functional food has never been studied as adjuvant for conventional therapeutics nor as an adjunct. Thus, there are abundant causes for our caption.

### Pre-study Observation

Hypo-thyroiditis and drug dose response are individual-specific and outcome variability is marred with swings. This pathology down-regulates thymus function; and up-regulates it in the status of hyper-thyroiditis or in over-drugging; monitoring is expensive and requires skilled manpower; and additionally, HRT does not lead to restoration of libido that is down-turned in the status of hypothyroiditis (own unpublished data). It also leads to

accumulation of 'brown adipose' which dose is not reduced nor the associated issues wane with HRT introduction, ... etc. Our decade long use of such functional food *which are, caffeic & Cinnamic acids*; i.e., 'active pharmaceutical ingredients' as adjunct with Levo-Thyroxin ('n' number; variety of cases) has been fruitful in every case for the clinician-patient combine. Such observation propels us to make a computation model-based validation of the observed; i.e., this study is a bottom-up model. No computational studies (In-Silico) have thus far been made involving our candidate compounds or the whole herbs.

Goiter has always been treated as out-patient malady handled by specialist clinicians. Officially, it has never been considered for at home tele-nursing and in reality, it is marked by (i) at home hapazard care (ii) tele-consultation; however, trained nurses/dieticians are being discounted in full. Threshold cases demand the attentive eagle eyes of a trained nurse. Retaining a case indefinitely at threshold level with functional foods is a victory for science. Such services to the afflicted can efficiently be extended *via* tele-route by the nursing community. A framework is not needed. Yet, as a concept, it is nowhere near the horizon.

### Objective

*OPEN AGENDA*: to pursue such observation, a poly-geography-based multi-national inter-disciplinary team focuses on the candidate foods which are locally available, economic, systemic and with historical other uses, i.e., safe 'Functional Food' that can be used with or without HRT (assessment based at presentation) with profit for all stakeholders, especially including 'commerce cajoled care'. *ENVELOPED AGENDA*: Being (a) ennobling the family physician (b) family welfare; being the dual pronged of immediate short term (c) drug discovery targeted computational study of (i) *caffeic acid* (ii) *Cinnamic acid*, being for the long term.

### Materials and Methods

#### Target Gene

Thyroid Stimulating Hormone (TSH) is the (dominant) candidate of goiter pathophysiology. It is taken as the target gene; it has got 7 unique chains. 205 kDa.  $C_{16}H_{22}N_6O_4$ . Figure 1 shows the 3D-structure of the TSH (Duan et al., 2022). Chain 'A' is taken as it is appropriate & logical in sync. with current Standard Operation Procedure.

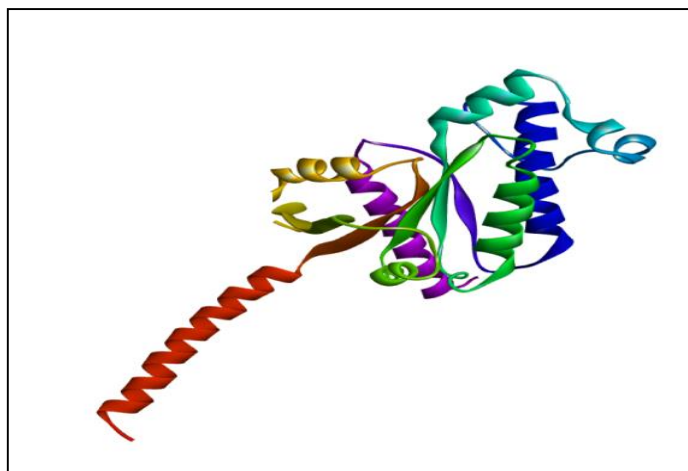


Figure 1. 3D-structure of TSH

#### Structure Selection

Protein structure of the TSH has been selected from the PDB (Protein Data Bank) database (Berman et al., 2000).

#### Drug Selection and Structure Finding

(i) Caffeic acid and (ii) Cinnamic acid are the two drug candidate compounds.

The respective structures were downloaded from PubChem database (Sunghwan et al., 2016) in SDF file format and converted into .pdb format in Discovery studio software.

- (i) Molar mass: 180 g/mol. Formula:  $C_9H_8O_4$ ; (hydroxycinnamic group), Figure 2.
- (ii) Molar mass: 148 g/mol ; Formula:  $C_9H_8O_2$  (-same-), Figure 3.

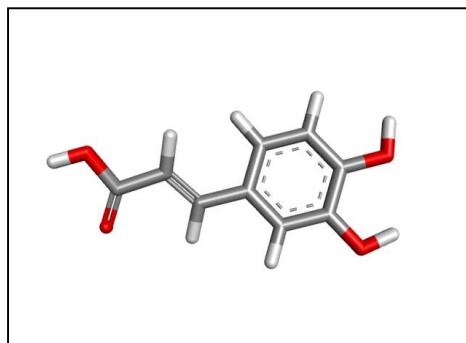


Figure 2. 3D-structure of caffeic acid.

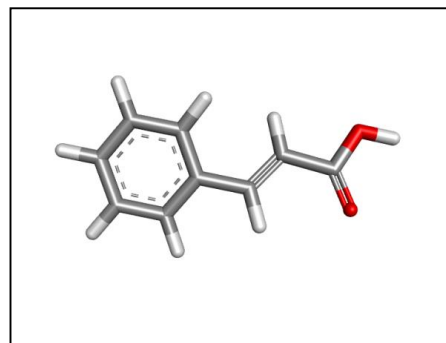


Figure 3. 3D-structure of cinnamic acid

### Binding Sites' Selection

CASTP web server has been used to find the binding sites of the protein structures (Binkowski et al., 2003).

### Serotypes' Structure Selection

Chain A of the PDB structure/s is necessary for *in-silico* investigations. For TSH, PDB ID 7XW6 has been taken.

### Molecular Docking with Serotypes' Structures

TSH is docked at the (predicted) binding sites using Autodock 4.2 tool (Faizul et al., 2012).

### Binding Sites

The binding sites of the protein were predicted by using the CASTp webserver. For TSH with PDB ID 7XW6 (Chain A is selected for the study) the resolution is 2.78 Å. The binding sites predicted are: GLU14,ALA15,ALA16,VAL17,ALA18,ALA19,GLU21,LEU35,LYS36,SER39,ALA64,PRO68,GLN69,VAL70,SER71,PHE72,SER125,GLY126,PRO127.

### Molecular Docking

For molecular docking on Autodock 4.2 tool, the grid box values for TSH protein taken are X-56, Y-56 and Z-66. Caffeic acid and Cinnamic acid were docked against the TSH protein. Table 1 shows the detailed information about the compounds taken for study. Table 2 shows the

docking results. Caffeic acid has a binding affinity of -5.09 kcal/Mol with TSH protein with 6 no. of H-bond-forming residues (details in Table 1). Cinnamic acid has a binding affinity of -5.04 kcal/Mol with TSH protein with 4 no. of H-bond forming residues, Figures 4, 5 and Figures 6, 7.

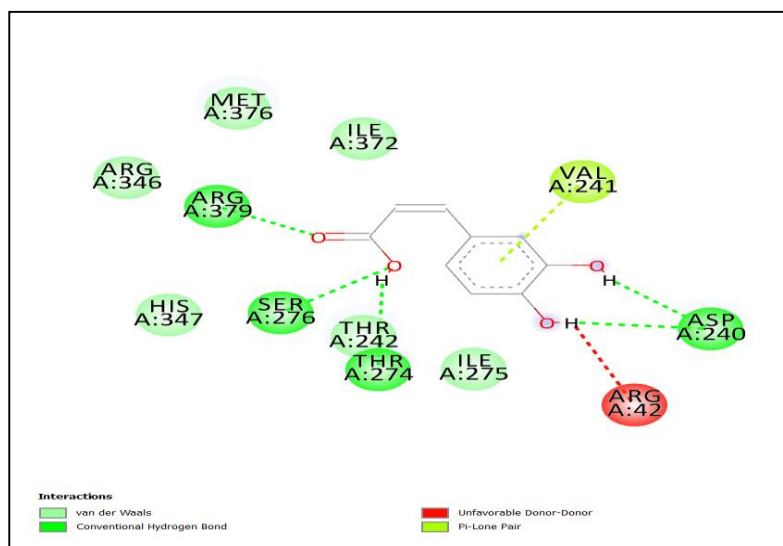
Thymoglobulin is a large, stable, very complex globular member with 7 chains. We have taken chain 'A' only, as it is adequately representative of initial work. In pharmacology and therapeutics, the non-toxic drug is the champion (stakeholder's choice). Historically, line graphs of the atomic composition of compounds whence juxtaposed the combined architecture crassly indicate synergy or anti-synergy. Figure 8 juxtaposes the molecular graph of TSH & Cinnamic acid. Crass synergy is suggested. Both graphs terminate at O atom of identical number. This may indicate conjugation with the globulin, disassociation and/or liberation of the O and N atoms, formation of NO resulting in process scavenging. A direct action of cinnamic acid on TSH is also apparent. Cinnamic acid terminates radical chain reactions by donating electrons that react with radicals, forming stable products (Ugazio et al., 2008). Thus, a tool-based validation is warranted (this communication). Clinical advice by family physicians and nurses to consume the raw powders in pinch-full quantity is helping all cases irrespective of therapy school and drug-dose regimen (supporting info).

Table 1. Description of compounds; caffeic acid and cinnamic acid

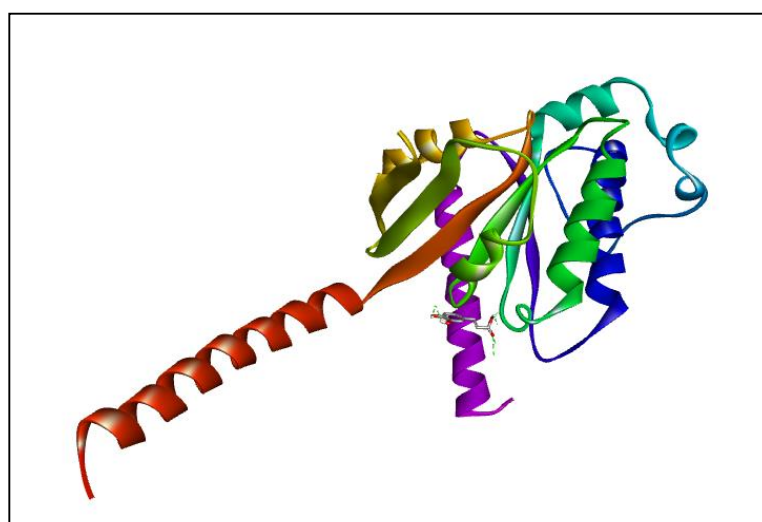
No.	Chemical name	Molecular formula	PMID	SMILE ID
1.	Caffeic acid	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>	689043	C1=CC(=C(C=C1C=CC(=O)O)O)O
2.	Cinnamic acid	C <sub>9</sub> H <sub>8</sub> O <sub>2</sub>	444539	C1=CC=C(C=C1)C=CC(=O)O

**Table 2. Docking of compounds; caffeic acid and cinnamic acid with TSH (thyroid stimulating hormone) protein (PDB ID- 7XW6)**

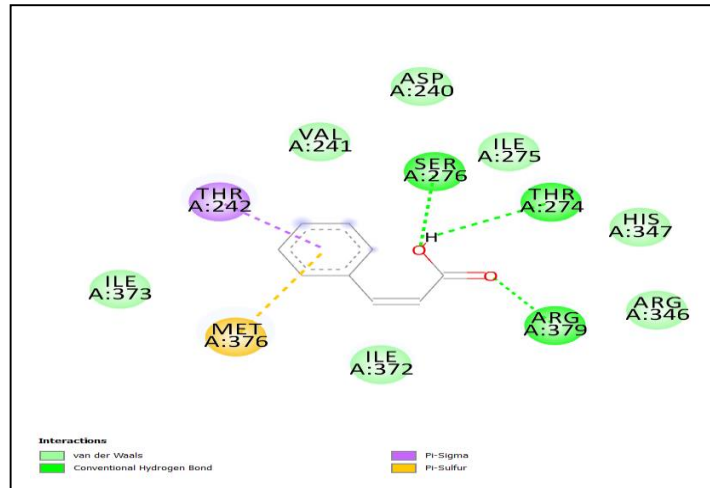
No.	Compound	Binding energy (kcal/Mol)	Ligand efficiency	Inhibition constant ( $\mu\text{m}$ )	No. of H-bonds	H-bond forming residues	Average distance of H-bonds ( $\text{\AA}$ )
1.	Caffeic acid	-5.09	-0.39	186.66	6	SER276, ARG379, THR374, ASP240,	2.164618333
2.	Cinnamic acid	-5.04	-0.46	200.5	4	SER276, ARG379, THR274	2.715811667



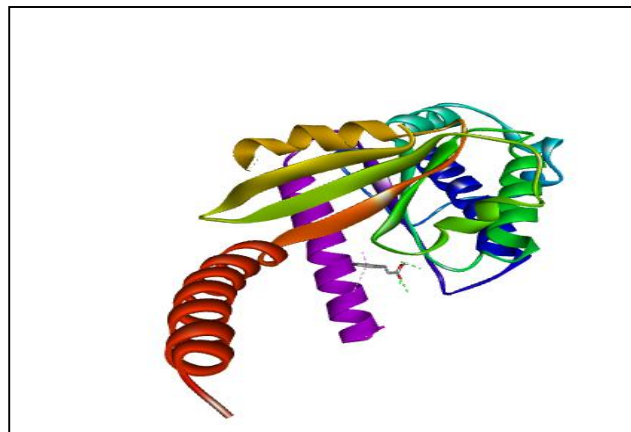
**Figure 4. 2D interaction of caffeic acid and TSH (thyroid stimulating hormone) protein (PDB ID- 7XW6)**



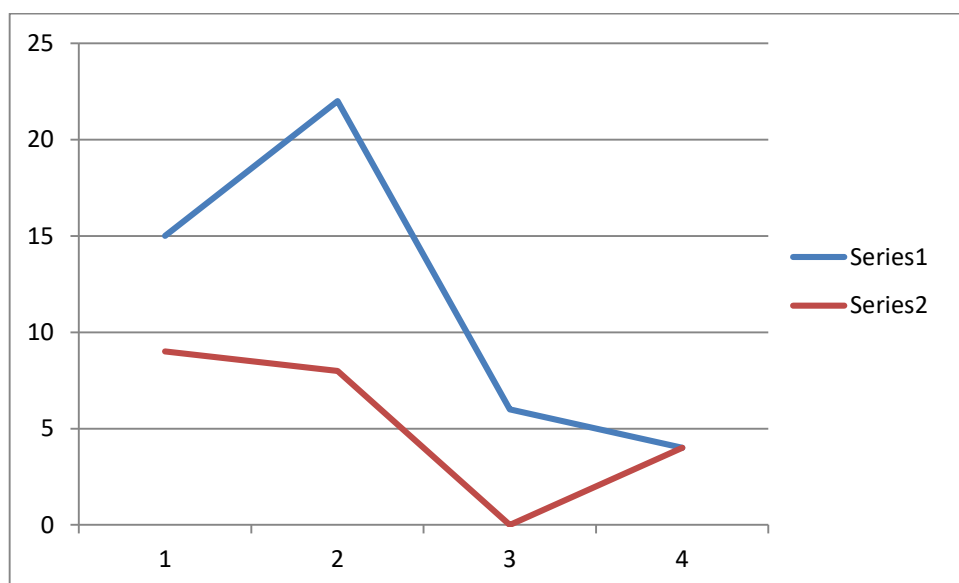
**Figure 5. 3D interaction of caffeic acid and TSH (thyroid stimulating hormone) protein (PDB ID- 7XW6)**



**Figure 6. 2D interaction of cinnamic acid and TSH (thyroid stimulating hormone) protein (PDB ID- 7XW6)**



**Figure 7. 3D interaction of cinnamic acid and TSH (thyroid stimulating hormone) protein (PDB ID- 7XW6)**



**Figure 8. Line graph- series -1: TSH = C<sub>16</sub>H<sub>22</sub>N<sub>6</sub>O<sub>4</sub>; series -2: hydrocinnamic/caffeic acid = C<sub>9</sub>H<sub>8</sub>O<sub>4</sub>**

### Toxicity Test

TSH and acids were run on the Pro-Tox tool (Kiss et al., 2012). Either transpire as non-toxic, Table 3.

**Table 3. Toxicity of compounds via ProTox-II tool**

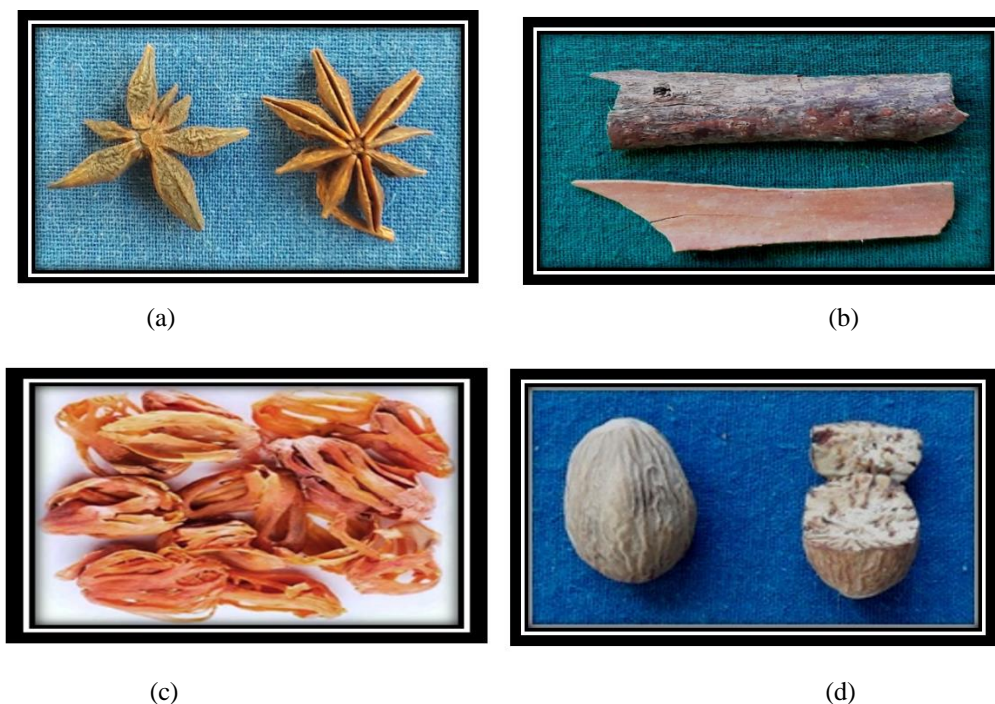
S.N.	Compound	Tool	Toxic/Non-toxic
1.	Caffeic acid	ProTox-II	Non-toxic
2.	Cinnamic acid	ProTox-II	Non-toxic

### Results

(i) *caffeic acid* and (ii) *cinnamic acid* corresponding to (phenolic~hydrocinnamic gr) indicate a clear 'likeness' for binding/docking onto TSH. Also, these compounds are non-toxic and synergic.

### Target Functional Foods

Cinnamic acid and bio-similars having identical action on human physiology are abundantly available in spices, as shown in Figure 9 (a-d). These 'functional foods' and sister cultivars are natural products between the 40<sup>th</sup> degree and the Equator of either hemispheres (wherein goiter is also on the gallop). Furthermore, cinnamic-acid derivatives are well known to antagonize gut pathogens and have salutary effect on *Akkermansia muciniphila* as well as on bile acids; i.e., overall gut biome friendly (Fernandez et al., 2021). Either of these organic acids assists and even up-regulate triosinase lipase, which is essential in thyroid hormone production (Kohlmeier, 2015). Sun-dried hand-ground powders of the neat whole herbs can be orally taken for prophylaxis and therapeutics. Therefore, we have focused on such common yet rich in drug moiety sources as 'target specific functional foods' with the intent to attract the attention of family physicians.



**Figure 9. (a) Star Anise is the dried fruit of *Illicium verum* tree (b) Cinnamon bark, Indian, wild. (c) Javitri//flower, (*Myristica fragrans*). (d) Javitri//fruit, (*Myristica fragrans*),**

### Discussion

Thymoglobulin needs iodination action for synthesis of T3, ... etc. (Harrison's Principles of Internal Medicine, 2019; OTBM Sec-13). Now, 'I' is metallic; element; Lewis salt; isotopic yet a halogen which makes it very effulgent in combination (including corrosives and carcinogens, ... etc., *in-vivo*). Iodination of thyroid

hormone is essential in homo sapiens life cycle. Failure has been related to bio-availability of anti-TPO (anti{thyo}peroxidase); systemic and/or intake-induced (Kowalska et al., 2021). TPO victoriously antagonizes anti-TPO. Hydroxycinnamic-acid derivatives and group included - reduce obesity and curtail-associated adverse health complications. Obesity

is associated with hypo-thyroids (Alam et al., 2016). Also, brown adipose is aspected the more (own unpublished data). So, our assisted hypothesis (stands on the broad shoulders of pre-workers) is that cinnamic acid derivatives (efficiently alter back and forth as polar and non-polar isomers = versatile; physiology-need dependent) well assist in the antagonization of anti-TPO in the status of thyroid. Pathophysiology or in threshold goiter and thus help conventional therapies; systemic iodine uptake. Hence, there are causes for our caption and objectives.

Hydrophilic amino acids are polar, while hydrophobic amino acids are non-polar. TSH's receptor domain is large (concave surface architecture), Leucine rich and hydrophobic (Zutinic et al., 2020). Cinnamic acid derivatives can be polar & non-polar. ARG; Thr; SER; ASP are hydrophilic; thus, firm bonding affinity and efficient donation are being noted. The high inhibition constant with a 2-2.5 Å distance of the H bond further affirms the likeness to yield nice therapeutic results. The half-life of T<sub>3</sub> is about 2.5 days, while the half-life of T<sub>4</sub> is about 6.5 days (Mezei et al., 2020), while the Cinnamic group's is maximum for 75minutes (Bin et.al., 2015). Hence these whence given sub-lingual, daily, repeatedly optimum results are reported.

Goiter strikes occur in prime age groups (anabolic stage). Due to life-style changes worldwide, goiter is on the gallop-resulting in colossus loss of work hours. Therefore, daily oral intake of raw herbs may also be fruitful (mini doses). Nice to be introduced by nurses under guidance of the family physician even in remote rural areas.

### Home-made – Hand-made (FFs)

Procure fresh raw ingredients from the market. All items as in Figure 9 (a-d) should be in equal measures (say 50gms each). Cut every item into pieces (avoid squeezing or loss of juice or sap), then sun-dry it to brittleness. Crush with pestle. Then, powderize/pulverize using mini high-speed home grinder. Open cover only after 15-20 minutes. Gather the powder. Screen with ordinary flour screen mesh. Fill in gelatin capsules or use therapeutic spoons to swallow post prandial or as per our suggested doses.

### Suggested Doses

(Prophylactic functional food) 1gm per dose OD (once daily) three days per week of all the three herbs

admixed well and taken together with potable water pre- or post-prandial calculated @ 60kg of body wt. BEST: ½ of above per dose sub-lingual 6 times/day.

(Therapeutic functional food): Same as above BID (*twice a day*). Best when taken sub-lingual between 30 to 45 minutes after conventional prescription drug.

(Fixed dose): Sun-dry all the three herbs to moisture content < 2%, w/w; pulverize in mixer-grinder (domestic m/c ok); fill in empty transparent gelatin capsule shells of size no.1 @ 100mg/shell and size no. 0 @ 330mg/shell. Use as per clinical indication; pathological staging. Approximate shelf life is 2yrs at full potency.

### Implications for Nursing

General implications include (i) completely new opportunities for learning and skill development, (ii) employment, (iii) public service, (iv) a hitherto new vestibule between healthcare industry & drug development, (v) new opportunities also for banking and financing in investors for assured gainful green field investments, (vi) remain effulgent about the role of FFs alongside HRT; toxic and/or repurposed therapeutics, and (vii) nurses can play an important role in defeating goiter. Specific implications include (i) remaining observant about the changes that a goiter patient's throat architecture undergoes with the FFs as are reported and discussed in this transaction – with or without HRT, (ii) documenting any hematological and biochemical slow or swing or delayed changes if any, (iii) in the absence of 'practice-&-intervention' framework (a) self-design individual case specific dos-&-do nots, (b) maintaining visual & written records methodically with tape and camera, (c) revisit the records and co-relate with the actual physical status of the patient, (d) physically examine the patient, and (e) discuss with treating clinicians and/or any competent physiological technician, (f) document all biological parameters regularly *such as*, hematological, biochemical, stool and urine; pulse/BP/O<sub>2</sub>; sleep; tongue; appetite; digestion/farting/colonic worms; dermal-icterus; small joint pain, ... etc., (g) put everything in public domain, and (h) invite the attention of drug discovering scientists towards possible 'smart starting material' for related drug discovery.

### Conclusion

While even non-fixed sub-lingual dose of such



compounds indicate good results. Fixed dose also indicate affinity. These are safe. The whole herbs can also be used alongside conventional modern therapies (in any form and quantity) ‘to manage thyroid disorders’ as ‘holistic approach in clinical practices’. Therefore, specific hydro cinnamic group loaded represents the very ‘Functional Food’ candidates in the caption domain. The study is a ‘bottom-up model’ and is indicative, opening a nice, new scope for nursing.

### Acknowledgements

Thanks to: Red Cross Clinic; for providing platforms to do the modeling and long-period studies; To Dr. Debasis Misra (Director Apex Blood Bank); Skin Specialist Capital Hospital cum Post Graduate Research

### REFERENCES

- Alam, M.A., Subhan, N., Hemayet, H., Murad, H., Reza, H.M., Rahman, M.M., & Ullah, O. (2016). Hydroxycinnamic acid derivatives: A potential class of natural compounds for the management of lipid metabolism and obesity. *Nutrition & Metabolism*, 13, Art. (27). <https://doi.org/10.1186/s12986-016-0080-3>
- Al, Z.R.H., Zaman, K.E.E., Saqallah, F.G., Zakaria, F., Asif, M., Razak, K.N.A. (2022). Medicinal plants' proposed nanocomposites for the management of endocrine disorders. *Heliyon*, 18 (8,9), e10665. <https://doi:10.1016/j.heliyon.2022.e10665>
- Avicenna “ibnSina”. (c.11<sup>th</sup> A.D.) *On healthy living: Exercising, massaging, bathing, eating, drinking, sleeping and treating fatigue (canon of medicine)*. Paperback. Dr. Laleh Bakhtiar, Ed., 2012. Great Books of the Islamic World, Inc., ISBN 10 1567447937.
- Bae, J.M. (2021). Hormonal replacement therapy and risk of thyroid cancer in women: A meta-epidemiological analysis of prospective cohort studies. *Journal of Menopausal Medicine*, 27 (3), 141-145. <https://doi:10.6118/jmm.21023>
- Bartalena, L., Bogazzi, F., & Martino, E. (1996). Adverse effects of thyroid hormone preparations and antithyroid drugs. *Drug Safety*, 15 (1), 53-63. <https://pubmed.ncbi.nlm.nih.gov/8862963/>
- Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, N.L., & Bourne, P.E., (2000). The protein data bank. *Nucleic Acids Research*, 28 (1), 235-242. <https://doi.org/10.1093/nar/28.1.2355>
- Bhattacharya-a, Deepak. (2009). Depiction of human anatomy in Indian archaeology: A report. *Indian Journal of History of Sciences*, Indian National Science Academy, 44 (2), 313-322. [https://www.researchgate.net/publication/216148558\\_DEPICTION\\_of\\_HUMAN\\_ANATOMY\\_in\\_INDIAN\\_ARCHAEOLOGY\\_A\\_REPORT](https://www.researchgate.net/publication/216148558_DEPICTION_of_HUMAN_ANATOMY_in_INDIAN_ARCHAEOLOGY_A_REPORT)
- Bhattacharya-b, Deepak. (2014). Select palm leaf manuscripts of healthcare sciences. *Indian Journal of History of Science*, Indian National Science Academy, 49 (3), 294-297 (original, hoary antiquity). [https://www.academia.edu/3543627/ASTRONOMY\\_and\\_MATHEMATICS\\_SELECT\\_PALM\\_LEAF\\_MANUSCRIPTS\\_OF\\_INDIA](https://www.academia.edu/3543627/ASTRONOMY_and_MATHEMATICS_SELECT_PALM_LEAF_MANUSCRIPTS_OF_INDIA)
- Bhattacharya-c, Deepak. (2023). Sun stroke: Physiological mechanism and palliative intervention. *Jordan Journal of Nursing Research*, 2 (2), 1-2. <https://doi.org/10.14525/JJNR.v2i2.02>
- Bin, Ji, Yunli Zhao, Qili Zhang, Pei Wang, Jiao Guan, Rong Rong, & Zhiguo Yu. (2015). Simultaneous determination of cinnamaldehyde, cinnamic acid, and 2-methoxy cinnamic acid in rat whole blood after oral administration of volatile oil of cinnamoni ramulus by UHPLC-MS/MS: An application for a pharmacokinetic study. *J. Chromatogr B. Analyt Technol*, 1001, 107-13. <https://doi:10.1016/j.jchromb.2015.07.049>
- Binkowski, T.A., Naghibzadeh, S., & Liang J. (2003). CASTp: Computed atlas of surface topography of proteins. *Nucleic Acids Research*, 31 (12), 3352-3355.

### Funding or Sources of Financial Support

This study received no financial support from any source.

### Conflict of Interest

No conflict of interest is to be declared by the authors.

- <https://doi.org/10.1093/nar/gkg512>
- Cagnacci, A., & Venier, M. (2019). The controversial history of hormone replacement therapy. *Medicina* (Kaunas), 55 (9), 602. <https://doi:10.3390/medicina55090602>
- Cidian, Z.D. (2005). *Grand dictionary of Chinese traditional medicine* (2<sup>nd</sup> Edn). Shanghai Science & Technology Press, Shanghai. <https://www.amazon.com/Dictionary-Chinese-Traditional-Medicine-Zhongyao/dp/7532308421>
- Connelly, K.J., Park, J.J., & LaFranchi, S.H. 2022. History of the thyroid, *Hormone Research Paediatrics*, 95, 546-556. <https://doi.org/10.1159/000526621>
- Cooper, S.D., & Blair, Anton. (2016). The decade in clinical thyroid disease: An analysis of published literature. *Thyroid*, 26 (8), 993-1003. <https://doi:10.1089/thy.2016.0018>
- Duan, J., Xu, P., Luan, X., Ji, Y., Yuan, Q., He, X., Ye, J., Cheng, X., Jiang, H., Zhang, S., Jiang, Y., & Xu, H.E. (2022). *TSHR-Gs-M22 antibody-ML109 complex*, RSCB-PDB. <https://www.rcsb.org/structure/7XW6>
- Faizul, A., Arwa, M.M., & Ali, H.I. (2012). Molecular docking and prediction of pharmacokinetic properties of dual mechanism drugs that block MAO-B and adenosine A2A receptors for the treatment of Parkinson's disease. *Journal of Young Pharmacists*, 4 (3), 184-192. <https://doi.org/10.4103/0975-1483.100027>
- FAO. (1980). *Endemic goiter and endemic cretinism; iodine nutrition in health and disease*. AGRIS, Stanbury, J.B. & Hetzel, Eds. <https://agris.fao.org/agris-search/search.do?recordID=XF2015021667>
- Fernández, M.J., Porras, D., Petrov, P., Sagüillo, S.R., Mediavilla, M.V.G., Soluyanov, P., Flórez, S.M., Kiss, R., Sandor, M., Szalai, F.A., Gallego, J.G., Nistal, E., Jover, R., & Campos, S.S. (2021). The symbiotic combination of *Akkermansia muciniphila* and quercetin ameliorates early obesity and NAFLD through gut microbiota reshaping and bile acid metabolism modulation. *Antioxidants* (Basel), 10 (12). <https://doi.org/10.3390/antiox10122001>
- Harrison's Principles of Internal Medicine, 19<sup>th</sup> Edn. (2019). Chapter 378- *goiter and nodular diseases*. Authors: J. Larry Jameson, Susan J. Mandel, & Anthony P. Wheatman. ISBN 978-1-259-64403-0; MHID 1-259-64403-0
- Kiss, R., Sandor, M., Sandor, & Szalai, F.A., (2012). A public web service for drug discovery. *Journal of Cheminformatics*, 4 (1), 1. <https://doi.org/10.1186/1758-2946-4-S1-P17>
- Kohlmeier, M. (2015). *Nutrient metabolism structures, functions and genes*. 2<sup>nd</sup> Edn., Full Book, Elsevier. ISBN:9780123877888
- Kotwal, Atul., Ritu, P., & Qadeer, I. (2007). Goiter and other iodine deficiency disorders: A systematic review of epidemiological studies to deconstruct the complex web. *Archives of Medical Research*, 38 (1), 1-14. <https://doi.org/10.1016/j.arcmed.2006.08.006>
- Kowalska, E.H., Agnieszka, A.K., Bartuzi, D., Pilat, J., & Urzula, G.-D. (2021). Some dietary phenolic compounds can activate thyroid peroxidase and inhibit lipoxygenase: Preliminary study in the model systems. *International Journal of Molecular Science*, 22 (10), 5108. <https://doi:10.3390/ijms22105108>
- Loyal, Chaker, Bianco, A.C., Jonklaas, J., & Peeters, R.P. (2017). Hypothyroidism. *The Lancet*, 90 (10101), 1550-1562. [https://doi.org/10.1016/S0140-6736\(17\)30703-1](https://doi.org/10.1016/S0140-6736(17)30703-1)
- Lee, C.H., & Chiu, J.H. (2021). Goiter disease in traditional Chinese medicine: Modern insight into ancient wisdom. *Journal of the Chinese Medical Association*, 84 (6), 577-579. <https://doi:10.1097/JCMA.0000000000000547> & <https://europepmc.org/article/med/34061810>
- Mathew, P., Jasleen, K., Prashanth R., & Kristina, F. (2023). *Hyperthyroidism (Nursing)*. StatPearls [Internet]. T. Island, Florida. <https://www.ncbi.nlm.nih.gov/books/NBK568782/>
- Mezei, Mihaly, Baliram, R.K., Ali, M.R., Zaidi, M., Davies, T.F., & Latif, R. (2020). The human TSHβ subunit proteins and their binding sites on the TSH receptor using molecular dynamics simulation. *Endocrinology*, 161 (9), 125. <https://doi:10.1210/endo/bqaa125>
- Niazi, A.S., Kalra, S., Irfan, A., & Islam. (2011). Thyroidology over the ages. *Indian J. Endocrinology & Metabolism*, 15 (Suppl. 2), S121-S126. <https://doi:10.4103/2230-8210.83347>
- Olson, E., Wintheiser, G., Wolfe, K.M., Droessler, J., & Silberstein, P.T. (2019). Epidemiology of thyroid cancer: A review of the national cancer database, 2000-2013. *Cureus*, 11 (2), e4127. <https://doi:10.7759/cureus.4127>
- Oxford Text Book of Medicine-OTBM. *Endocrine diseases*. Section 13, Vol. III, 6<sup>th</sup> Edn., Oxf. Uni. Press. <https://global.oup.com/academic/product/oxford-textbook-of-medicine-9780198746690?cc=us&lang=en&>

- Read, Bernard E. (1936). Chinese medical plants from the pen ts'ao kang mu, c. 1596 A.D. *Peaking, Natural History Bulletin*. See also 3<sup>rd</sup> Edition of a Botanical, Chemical and Pharmacological Reference List. Ed. and Reproduced (1977) in Chinese Medicine Series, Taipei: Southern Materials Center. ISBN:0598606637, 9780598606631
- Siddiqi, M.Z., (1959). *Studies in Arabic and Persian medical literature*. Full Book, Calcutta University, India.
- Sunghwan, K., Thiessen, P.A., Bolton, E.E., Chen, J., Fu, G., Gindulyte, A., Han, L., He, J., He, S., Shoemaker, A, B., Wang, J, Yu, Bo., Zhang, J., & Bryant, S.H. (2016). PubChem substance and compound databases. *Nucleic Acids Research*, 44 (D1), D1202-D1213. <https://doi.org/10.1093/nar/gkv951>
- Szkudlinski, M.W., Fremont, V., Catherine, R., & Weintraub, B.D. (2002). Thyroid-stimulating hormone and thyroid-stimulating hormone receptor structure-function relationships. *Physiological Review*, 82 (2), 473-502. <https://doi:10.1152/physrev.00031.2001>
- Taïbi, K., Ait Abderrahim, L., Helal, F., & Hadji, K. (2021). Ethnopharmacological study of herbal remedies used for the management of thyroid disorders in Algeria. *Saudi Pharmaceutical Journal*, 29 (1), 43-52. <https://doi:10.1016/j.jsps.2020.12.004>
- Taylor, P.N., Albrecht, Diana, Scholz, Anna, Gutierrez-Buey, Gala, Lazarus, John H., Dayan, Colin M., & Okosieme, O.E. (2018). Global epidemiology of hyperthyroidism and hypothyroidism. *Nature Review Endocrinology*, 14, 301-316. <https://doi.org/10.1038/nrendo.2018.18>
- Ugazio, E., Carlotti, M.E., Sapino, S., Trotta, M., Vione, D., & Minero, C. (2008). Photodegradation of cinnamic acid in different media. *Journal of Dispersion Science & Technology*, 29, 641-652. <https://doi:10.1080/01932690701758491>
- WHO. (2014). *Goitre as a determinant of the prevalence and severity of iodine deficiency disorders in populations*. WHO/NMH/NHD/EPG/14.5. [https://apps.who.int/iris/bitstream/handle/10665/133706/WHO\\_NM\\_H\\_NHD\\_EPG\\_14.5\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/133706/WHO_NM_H_NHD_EPG_14.5_eng.pdf)
- Zutinic, A., Blauw, G.J., Pijl, H., Ballieux, B.E., Westendorp, R.G.J., Roelfsema, F., & Van Heemst, D. (2020). Circulating thyroid hormone profile in response to a triiodothyronine challenge in familial longevity. *Journal of the Endocrine Society*, 4 (10), 117. <https://doi:10.1210/jendso/bvaa11>