Published online in http://ijam.co.in ISSN No: 0976-5921

International Journal of Ayurvedic Medicine, Vol 13 (2), 328-333

Role of *Santha Santhrothaya Mathirai* (SSM), A Siddha Herbo-Mineral Formulation in the Management of Hepatic Disorders – A Review Study

Review Article

Shanmugapriya P[1*], Jeeva Gladys[2], Subathra T[3], Neethi B[4], Ramamurthy M[5], Murugesan M[6], Thamodaran S[7]

1. Associate Professor, Department of Nanju Maruthuvam, 3. Research Scholar, Department of Nanju Maruthuvam, 4. PG Scholar, Department of Nanju Maruthuvam, 5. Associate Professor, Department of Noi Nadal, 6. Former Dean, National Institute of Siddha, Chennai. India.
2. Lecturer, Velumailu Siddha Medical College, Sriperumbudur, Chennai. India.
7. Lecturer, Government Siddha Medical College, Arumbakkam, Chennai. India.

Abstract

Liver disorders share a larger disease burden of the world every year. Liver disorders are caused by toxic chemicals, drugs, viruses (hepatitis A, B, C, D, and E), excess alcohol intake etc., and are ranked among the top ten killer diseases in India. With only meagre number of dependable drugs available for hepatoprotective action, the present scenario has created a stage for scientific evaluation of traditional medicines in the treatment of liver disorders. The Siddha literature has provided a lot of herbal and herbo- mineral formulations as indications for the management of liver disorders. Though several studies have been done on hepatoprotective herbs in recent years, very minimal researches have been done on herbo-mineral formulations. Therefore this review focuses on the literature search involving both traditional ancient Siddha texts as well as recent researches for hepatoprotective activity on all the ingredients of *Santha Santhrodhaya Mathirai (SSM)* a classical herbo-mineral formulation that has been indicated for the treatment of *Pitha Suram* and other biliary disorders.

Key Words: *Santha Santhrodhaya Mathirai (SSM), H*epatoprotective, *Siddha,* Herbo-mineral drug, Liver disorder, Phytochemicals.

Introduction

Liver is a major metabolic organ which plays a pivotal role in provision of nutrients to the blood and excretion of toxins. Liver disorders are caused by toxic chemicals, drugs, viruses (hepatitis A, B, C, D, E), excess alcohol intake etc., and are ranked among the top ten killer diseases in India (1,2). Approximately, 2 million deaths per year throughout the globe were due to Liver disorders. The top priorities among the cause of death were complications of cirrhosis, viral hepatitis and hepatocellular carcinoma (3). According to the data published in 2018 by WHO, Deaths due to Liver disorders reached 264,193 or 3.00% of total deaths in India (4).

According to *Siddha* pathology, liver disorders are caused due to deranged *pitha* humor (*Pitha Dhosham* - aggravated/stagnated) and may result in symptoms such as giddiness, vomiting, headache, poor digestion and pigmentation problems. These symptoms are best correlated with those of bilious disorders (5). With only meagre number of dependable drugs available for hepatoprotective action, the present scenario has created a stage for scientific evaluation of traditional medicines in the treatment of liver disorders.

The therapeutics of *Siddha* system consists of herbal, metallic, mineral and animal origin. The literature describes that when there is a failure in disease response to drugs of herbal origin, metallic and mineral preparations can conquer the illness (5). Regarding Hepatoprotective drugs, numerous single herbs like *Keezhanelli* (*Phyllanthus niruri* Linn.), *Avuri* (*Indigofera tinctoria* Linn.), *Nellikai* (*Phyllanthus amarus* Schumach. & Thonn.), *Kadukkai* (*Terminalia chebula* Retz.) and also several poly-herbal formulations such as *Karisalai chooranam*, *Bavana kadukkai Mathirai*, *Manjal Noi Kudineer*, etc. were mentioned in *Siddha* literature and manuscripts. One among them, *Santha Santhrodhaya Mathirai (SSM)* is a classical herbo mineral formulation, mentioned in *Siddha Vaidhya Thirattu* and *Kannusamy Parambarai Vaithiyam* indicated for the treatment of *Pitha Suram* and other diseases associated with *Pitham* (biliary disorder) (6,7). The ingredients of *SSM* are *Pooram* (Mercurous chloride / Calomel), *Vengaaram* (Borax), *Kappu Manjal* (*Curcuma longa* Linn.) and *Elumicham pazhasaaru* (Juice of *Citrus limon* (L.) Burm.f.) which helps in enhancing liver functions (8). *Santha Santhrodhaya Mathirai (SSM)* derives its name due to its biological action of alleviating the aggravated

*** Corresponding Author:**
Shanmugapriya P
Associate Professor,
Department of Nanju Maruthuvam,
National Institute of Siddha,
Chennai-47 India.
Email Id: sppriyaathamu@gmail.com

Pitham humor (*Santham* means 'alleviate') which is considered as a 'fire' that is responsible for Liver disorders. *Santhrodhayam* means 'the coolant effect' which is attributed due to alleviated *Pitham*. *SSM* is in wide clinical usage among *Siddha* practitioners to treat bilious disorders and jaundice in particular for many decades. It's high time to emphasize the scientific background of *SSM* to prove its significance as a hepatoprotective formulation; hence we reviewed the literature regarding the ingredients of *SSM* in this present work.

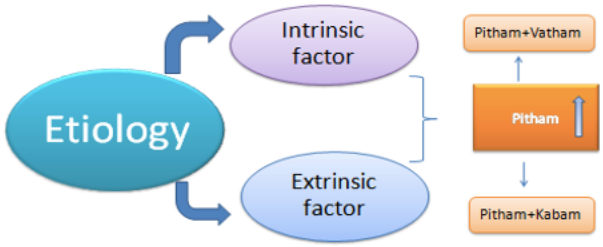
Materials and Methods

The literature search involved the *Siddha* classical literature such as *Siddha Vaidhya Thirattu, Kannusamy Parambarai Vaithiyam, Gunapadam* (*Siddha* Materia Medica) of herbal and mineral origin, and also the search extended to the recent literary analysis of these herbo mineral drugs based on internet resources in Google scholar, Scopus, Science direct, Pub med, Elsevier and modern text books by reputed authors.

Siddha pathology of Liver disorders

According to *Siddha* principles, *Mukkutram* i.e., *Vatham* (wind), *Pitham* (fire) and *Kapham* (water) are the three bodily humors which are responsible for the normal physiological condition of the body. If any one of these three humors deviates from its standard ratio ie.,1:1/2:1/4 *maathirai* respectively, it gives rise to various pathological changes in the body resulting in diseased conditions. According to *Siddha* system, both internal and external factors such as alterations in diet, lifestyle, and behavioral patterns, continually influence the state of the three *Dhoshams* inside our body and they account for the well-being of an individual (Fig-1). The appearance of any symptom of ill health is the first sign of the individual having lost some nature of sensitivity and balance in relation to the nature of his constitution. Thus, *Kalleral Noigal* (Liver disorders) is caused by excessive activity of *Pitha Dhosham*. This *dhosham* is associated with other humors - *Vatham* and *Kapham* along with *Viyaanan,* a type of *Vaayu* with spreading nature (9).

Figure-1: Siddha pathology of iver disordrs



Preparation of SSM

The purified *Pooram* (Calomel) (100gm), *Vengaaram* (Borax) (50gm) and *Kappu Manjal* (*Curcuma longa* Linn.) (300gm) were powdered separately and mixed uniformly in a *kalvam* (Black stone Mortar). To this, *Elumicham pazhasaaru* (Juice of *Citrus limon* (L.)Burm.f.) (1350ml) was added constantly and triturated for 12 hours and made into a pill-rolling pasty consistency. It is then made into pepper-sized pills (60mg) and dried in shade. The pills are indicated to be administered with honey as an adjuvant for the management of *Pitha Suram* (10).

Analysis of SSM based on "The six tastes concept" (11)

According to *Siddha* pathology, liver disorders may be caused due to aggravated or stagnated *Pitham*. In order to pacify an aggravated *Pitha Dhosham*, sweet, bitter, astringent tastes are to be used medicinally and to stimulate a stagnated *Pitha Dhosham,* salt, sour and pungent tastes are preferred (12). Since *SSM* is a combination of all the six tastes as tabulated above, it can be used for both aggravated as well as stagnated *Pitha Dhosham* that causes various hepatic disorders (Table-1).

Table-1: Analysis of SSM based on "The six tastes concept"

S.NO	Ingredients	Taste (*Suvai*)
1	*Vengaaram* (Borax)	Sweet, astringent
2	*Pooram* (Calomel)	Salt, pungent
3	*KappuManjal* (*Curcuma longa* Linn.)	Pungent, bitter
4	*Elumicham pazham* (*Citrus limon* (L.) Burm.f.)	Sour

Scientific analysis of ingredients of SSM

***Kappu Manjal* (*Curcuma longa* Linn.):**

Curcuma longa Linn. contains phytochemicals such as turmerones, turmerol, curcuminoids, curcumin, demethoxycurcumin and bisdemethoxycurcumin, as well as volatile oils limonne, caryophylline and zingiberone α-phellandrene (1%), sabinene (0.6%), cineol zingiberene (25%) and sesquiterpines (53%) (6). Curlone, a phytochemical from dried rhizome, is used against hepatitis. Curcuminoids (13) show significant antihepatotoxic action. It has carminative, stimulant, hepato tonic, aromatic, anthelmentic, anti-inflammatory, febrifuge, appetizer, haematinic, antiperiodic, expectorant, stomachic, anodyne and diuretic properties (14). Several therapeutic activities have been attributed to *Curcuma longa* Linn. since 1900 BC, for a variety of diseases, including liver disorders. Its hepatoprotective property is due to the main active ingredient Curcumin, which is obtained from this plant, whose structure was determined as diferuloylmethane in 1910 (15).

A study reveals the antioxidant effect of curcumin and concluded that it causes significant reduction in the lipid peroxidation in CCl_4treated rats (16). A.Ch. Pulla Reddy et. al.1994, carried out an experimental research on Wistar rats which were fed a control diet or the control diet supplemented with 1% (by weight) turmeric for 10 weeks. They established that the level of superoxide dismutase, catalase and glutathione

peroxidase was increased and also the level of lipid peroxidation in liver tissue was decreased (17). I.Dairaku et.al. demonstrated that curcumin has a wide range of antiviral property through inhibitory activity against Inosine monophosphate dehydrogenase (IMPDH) which is suggested as a therapeutic target for antiviral and anticancer compounds. Curcumin acts in either noncompetitive or competitive manner or it is suggested as a potent antiviral compound against different viruses (18).

H. J. Kim,et al.,2009.,studied the antiviral effect of aqueous extract of *Curcuma longa* Linn. rhizome against HBV in Hep G 2.2.15 cells, containing HBV genomes that showed regression of HBsAg secretion and suppressed the HBV replication by suppressing HBV particles production from liver cells without any cytotoxic effect(19). Rivera-Espinoza Y et al.2009.,in their research work on curcumin has revealed that it has anti-inflammatory, anti-oxidant, antifungal, antibacterial and anticancer activities. Curcumin possess to restrain nuclear factor-kappa B, thereby given a rational molecular basis to use it in hepatic disorders by modulating several pro-inflammatory and pro fibrotic cytokines as well as their anti-oxidant properties (15).

The bioactive effects of *Curcuma longa* Linn. on hepato-biliary disease were grouped as curcuminoids and non curcuminoids (20). Curcumin is the major curcuminoids, about which we discussed above. Here let us focus on four important non-curcuminoids namely β-Elemene, Germacrone, Ar-Turmerone, and Bisacurone. Previous two have both hepatoprotective and anti-cancer activity. Ar-Tumerone possesses cholagogic effect in addition. Bisacurone also shows hepatoprotective effects on liver injury induced by ethanol and cholestasis (21).

Elumichai (Citrus limon (L.) Burm.f.)

Lemon fruit contains many important compounds such as phenolic compounds, mainly flavonoids, vitamins (vitamin C), minerals, dietary fiber, essential oil and carotenoids. The peel is richer in flavonoids, neo-eriocitin, neohesperidin and naringin (22). Oyedepo T.A et al., studied the antioxidant and hepatoprotective potentials of lemon and concluded that it has the ability to normalize the antioxidant enzymes and peroxidases of liver tissues against paracetamol induced hepatotoxicity (23).

The health benefits of *C. limon* (L.) Burm.f. is determined by its high content of phenolic compounds, primarily flavonoids like limocitrin, diosmin, hesperidin and phenolic acids like synapic, ferulic, p-hydroxybenzoic acids. The essential oil is loaded with bioactive mono terpenoids. In recent times, scientifically proven therapeutic activities of *C. limon* (L.) Burm.f. include anti-inflammatory, antimicrobial, anticancer and antiparasitic activities (24).

Robert Jacob et al., reported that the phytoconstituents of lemon such as citrus limonoids have potent anticancer activity in mice and were found to raise the significant amount of detoxifying enzymes (25). Study on hepatoprotective effect of *Citrus limon* (L.) Burm.f. fruit extract against Carbofuran induced toxicity in Wistar Rats by Sunil Kumar Jaiswal et al.2015, showed that rats pretreated with lemon juice prior to the exposure, caused significant recovery in the levels of the enzymes (AST, ALT and LDH) both in liver tissue and serum of rats which confirmed its hepatoprotective activity (26).

M. Pisoschi et al., suggested that ascorbic acid (vitamin C) present in lemon has an important role in biosynthesis of collagen and has wound healing property. It also helps in the absorption of iron, activation of immune response, and osteogenesis (27). Victor Antony Santiago et al., studied that supplementation with D-limonene has been shown (in rats) to turn around the hepatic fatty acid level besides non-alcoholic fatty Liver disorder (28). Lemon has been found to have protective effects on T cell-dependent hepatitis (29,30).

The below two ingredients, *Vengaaram* (Borax) and *Pooram* (Calomel) are mineral ingredients and the above explained herbal ingredients *Curcuma longa* Linn. and *Citrus limon* (L.) Burm.f. are pharmacologically studied to possess hepatoprotective action (31-34) as shown in Table-2.

Table-2: Pharmacological action of ingredients of *SSM*

S. No.	Ingredients (Tamil Name)	Chemical and botanical name	Pharmacological action
1	Purified *Vengaaram*	Sodium biborate (Borax)	Antioxidant, hepatoprotective (31)
2	Purified *Pooram*	Mercurous chloride (Calomel)	Antipyretic, Anti-inflammatory (32)
3	*Kappu Manjal*	*Curcuma longa* Linn.	Antioxidant, antiviral, antifungal, hepatoprotective (33)
4	*Elumicham pazhasaaru*	*Citrus limon* (L.) Burm.f.	Anti-inflammatory, antioxidant, hepatoprotective (34)

Vengaaram (Borax)

Borax is also known as sodium tetraborate. It is an important mineral and a salt of boric acid. It dissolves easily in water and it is white in colour. It occurs as a natural deposit. It is found in masses by evaporation of water, on shores of dried up lakes in India, Tibet and Nepal. Ince et al., 2010 and Nielsen et al., have claimed that boron limits oxidative damage by enhancing the body stores of glutathione, inhibiting ROS (Reacting Oxygen Species) and acts as a metabolic regulator in enzymatic systems (35,36).

Studies by Turkez et al. (2007) found that, boron compounds increased erythrocyte antioxidant level in human blood samples (37). In thiocetamide-induced hepatocellular carcinoma animals, it revealed that boron has beneficial effects on proliferating cell nuclear antigen index and ameliorating the oxidative stress (38). Another study on the cytotoxicity and negligible genotoxicity of borax and its ore to cultured mammalian cells showed that refined borax did not induce

neoplastic transformation in C3H/10T1/2 cells (39,40). Processed borax at therapeutic dose (22.5mg/kg) has shown better antidotal activity profile against aconite poisoning. It has been proved that processed borax reverse the cardio-toxic effects like premature heart beat and ventricular tachyarrhythmia (41).

***Pooram* (Mercurous Chloride / Calomel)**

There are several forms of mercury which may exist in inorganic state, metallic state, mercury vapor and mercurous mercury (Hg^{+}) or mercuric mercury (Hg^{++}) salts. The Pharmacokinetics, biological behavior and clinical significance of the various forms of mercury may differ depending on its chemical structure.

The *Pooram* (Calomel) also known as Mercurous chloride is insoluble in water. *Pooram* is said to possess laxative, tonic, antiseptic, germicide, diuretic, sialagogue, alterative, cholagogue and purgative properties (39). It has broad spectrum antimicrobial activity against gram positive and gram negative bacteria and also against skin pathogens (42).

In 1600, Calomel entered the medical practice as a mild and palatable form of mercury. In 1800 it was widely accepted as an "alterative" as it altered the overall constitution of the body. Calomel (mercurous chloride) was believed to stimulate the liver and gall bladder. Hence, it was used as a purgative and laxative medicine in the form of tablet and injection in the late 19th century. An extract of calomel, colocynth, jalap and gamboges was used historically according to the *United States Dispensatory* of 1918 and was found to be a safe cathartic that is highly efficient and useful in congestion of the portal circle and torpidity of the liver (32,43,44).

During the 18th and 19th centuries the British started using calomel throughout their empire and very soon it gets the eminence as "valiant medicine", as many practitioners prescribed it for bloodletting, enema and other purgatives for balancing the deranged humours of the body.

Discussion

The reverberating situation of mercurial toxicity and the indications of *SSM* given in Siddha literature for liver disorders along with its present day clinical usage has urged the investigator to undertake the literary search in this area and to validate the potency of *SSM*. This literature review involved extensive search on the ingredients of *Santha Santhrodhaya Mathirai* (*SSM*) which is a Siddha herbo mineral drug used for the treatment of hepatic disorders. In recent times, mercury based drugs are cautioned due to its toxic effects and studies by Saper et al., concluded that metallic preparations are toxic by determining the presence of heavy metals using XRF analysis (45). But these studies have not considered about the physico chemical structural changes of these metals that have occurred before and after purification process and none of the researches had included toxicological or clinical studies as evidence. In controversy, there also studies that declare that the herbo-mineral drugs are comparatively safe when they are properly prepared as per the standard manufacturing process mentioned in the literature. During the purification and preparatory processes, intense physico chemical changes are inflicted into the herbo-mineral drugs by using various herbs and diverse components and are made therapeutically effective (46).

Herbomineral formulations mentioned in Siddha system of medicine renders the elemental metals to be converted into assimilable and excretable metallic salt complexes. The possible reason for safety of *SSM* from heavy metal toxicity may be due to the fact of grinding it with lemon juice along with turmeric as treating the metals with herbal juices leads to reduction in particulate size even up to nano levels making them effective in low doses and enabling increased potency (47). Moreover, studies by Shanmugapriya et al., reveal that in-vivo acute toxicity study of *SSM* did not induce any clinical signs of toxicity up to a single high dose of 2000 mg/kg b.wt,. Therefore *SSM* can be classified under catalogue-5 according to the Globally harmonized system of classification of drugs and labeling of chemicals. Also the sub-acute toxicity study ensured the safety of *SSM* after repeated oral administration for 28 consecutive days. Therefore *SSM* can be considered to be a safe drug for therapeutic usage (34).

The advantages of herbo-mineral preparation over herbal drugs are the virtue of stability over longer duration, lower dosage requirement, easy storability, sustained availability and the possibility of reprocessing and reuse whereas plant and animal based drugs need to be discarded when they lose their shelf life. The metals and minerals which are considered to have less bioavailability are converted to forms that are relatively more bio-compatible by processing them with herbs during the purification and preparatory procedures (48). Previous studies on a mercurial compound called "Kajjalibhasma" by Sathya et al. also supports the fact that there was no genotoxicity in terms of mono nuclei induction or DNA damage and emphasize the safety of mercurial compounds for human usage (49).

Although *Pooram* (Mercurous chloride) is said to be toxic in many ways in its unpurified form as it was used in western medical history, According to Siddha literature, the preparation of *SSM* involves the use of organically purified mercurous chloride which is further potentiated with hepato tonics such as turmeric and lemon juice. Thus it is made perfectly suitable for liver disorders. Also studies reveal that exposure to even a very small amount of mercury could lead to the synthesis of specific metallothioneins that are small molecular weight peptides containing close to 20 and above cysteine amino acid units. The SH group very strongly complexes mercury and considered to play a central role in the physiology of heavy metal detoxification (50). Hence, mercury is bound to metallothionein which serves as a protection, as renal damage is caused only by unbound metal. Further, curcumin present in *Curcuma longa* Linn. is also found to act as a chelating agent and protects against mercury-induced hepatic damage (51). Therefore the purification process of mercurial compounds and the processing of drug completely transform the chemical structure

thereby rendering the drug, *SSM* therapeutically safe and effective for the treatment of liver disorders.

Conclusion

This literature review highlights the use of herbo-mineral formulations *SSM* for the management of liver disorders and the supremacy of mercurial compounds as catalytic agents. Although, the medicinal preparations mentioned in Siddha literature are time-tested standard preparations, it is need of the hour to document the standardization procedures by using sophisticated instrumental analysis to maintain quality control. Hence further studies on the scientific validation of *SSM* should be performed by adopting various analytical techniques. Clinical trials and documentation should also be carried out in the future to understand the safety and clinical efficacy of the traditional drugs.

Conflict of Interest:

There are no conflicts of interest.

References

1. Gupta B. M, Adarsh Bala1,Mueen Ahmed KK2,Ritu Gupta. Liver disorders: A scientometric study of publication outputs from India during 2003-2012.International Journal of Medicine and Public Health.2014; 4(1).
2. Mohamed Saleem T.S K, C. Madhusudhana Chetty, S. Ramkanth, V.S.T. Rajan, K. Mahesh Kumar, Gauthaman.Hepatoprotective Herbs – A Review. Int. J. Res. Pharm. Sci. 2010; 1(1); 1-5.
3. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol, January 2019;70(1);151-171.
4. http://www.worldlifeexpectancy.com/india-liver-disease dated 20.01.2022 time 10.05 IST
5. Anaivari R, Anandan.A Compendum of Siddha doctrine.1st Edition.Department of Indian medicine and Homoeopathy; 2005.
6. Kuppusamymudhaliyar K.N, Uthamarayan. K.S.SiddhaVaidhiyaThirattu. Chennai;Indian Medicine and Homoeopathy Department
7. Kannusamipillai. C.Parambaraivaithyam,. Chennai;Rathnanayakar and sons;2006.147p.
8. Thiyagarajan. R.Gunapadam Thathu Jeeva vakuppu part -2& 3. 4th edition.Chennai;Indian medicine and Homoeopathy department; 2004. 282-283pp , 435 -440pp.
9. KuppusamyMudhaliyar. K.N.Siddha Maruthuvam (Pothu). Chennai;Directorate of Indian Medicine and Homeopathy Publications;2012.338-372pp.
10. Kuppusamy Mudhaliyar K.N, Uthamarayan. K.S, SiddhaVaidhiyaThirattu.Chennai;Indian medicine and Homoeopathy Department;21p
11. Vaithiya Rathinam K.S. Murugesamuthaliar.Gunapadam First part.Chennai;Indian medicine and Homeopathy Department;160p
12. Pal Pandian.Siddhas Masters of the basics. Achala Siddha publications; NPT Offset press printers pvt ltd.; 2008.152p
13. The wealth of India Vol-2. New Delhi; National institute of science communication and information resources; 2001.286-287pp
14. Varier.P.S.Indian medicinal plants. A compendium of 500 species. 1997;Vol-2;259p.
15. Rivera-Espinoza Y, Muriel P.Pharmacological actions of curcumin in liver diseases or damage.Liver Int. Nov,2009;29(10);1457-66
16. Shu-Ju Wu et al. Curcumin or Saikosaponin a Improves Hepatic Antioxidant Capacity and Protects Against CCl_4-Induced Liver Injury in Rats. Journal of Medicinal Food. July 2008;11(2);224-229.
17. Pulla Reddy.A.Ch., Lokesh.B.R.Effect of dietary turmeric (*curcuma longa* L.) on iron-inducedlipid peroxidation in the rat liver.Food and Chemical Toxicology. 1994; 32(3); 279-283.
18. Dairaku.I, Han.Y, Yanaka.N, and Kato.N.Inhibitory effect of curcumin on IMP dehydrogenase, the target for anticancer and antiviral chemotherapy agents. Bioscience, Biotechnology and Biochemistry.2010;74(1);185–187.
19. Kim H. J., Yoo H. S., Kim J. C. et al.Antiviral effect of *Curcuma longa Linn* extract against hepatitis B virus replication.Journal of Ethnopharmacology. 2009;124(2);189–196.
20. Li S., Yuan W.,Deng G., Wang P., Yang P., and Aggarwal B.Chemical composition and product quality control of turmeric (Curcuma longa L.). Pharmaceutical Crops.2011;5(1); 28–54
21. An S, Jang E, Lee JH.Preclinical Evidence of *Curcuma longa* L. and Its Noncurcuminoid Constituents against Hepatobiliary Diseases: A Review. Evid Based Complement Alternat Med. 2020 Jul 28;8761435.
22. Yoshiaki MIYAKE et al.Characteristics of Antioxidative Flavonoid Glycosides in Lemon Fruit. Food Science and Technology International.1998;4;48-53.
23. Oyedepo T.A et al,.Antioxidant and Hepatoprotective Potentials of Lemon Juice and Sorghum Ogi (lemon-ogi) Mixture against Paracetamol-Induced Liver Damage in Rats. Advances in Life Science and Technology.2015;38
24. Klimek-Szczykutowicz M, Szopa A, Ekiert H,*Citrus limon* (Lemon) Phenomenon—A Review of the Chemistry, Pharmacological Properties, Applications in the Modern Pharmaceutical, Food, and Cosmetics Industries, and Biotechnological Studies. *Plants*. 2020; 9(1);119
25. Jacob R, Hasegawa S, and Gary Manners.The potential of Citrus limonoids as anticancer agents.Perishables Handling Quarterly. 2000; 102
26. Sunil Kumar Jaiswal, Vivek K.Gupta, Nikhat J.Siddiqi, Ravi S.Pandey, and Bechan Sharma Hepatoprotective Effect of Citrus limon Fruit Extract against Carbofuran Induced Toxicity in Wistar Rats. Chinese Journal of Biology.2015;10 .
27. Pisoschi, Danet A.F., and Kalinowski S. Ascorbic acid determination in commercial fruit juice samples by cyclic voltammetry. Journal of

Automated Methods and Management in Chemistry.2008;8.
28. Victor Antony Santiago J, Jayachitra J, Shenbagam M, Nalini N.Dietary d-limonene alleviates insulin resistance and oxidative stress-induced liver injury in high-fat diet and L-name-treated rats.Eur J Nutr. February 2012;51(1);57-68.
29. Sood S., Arora B., Bansal S.et al.Antioxidant, anti-inflammatory and analgesic potential of the Citrus decumana L. peelextract.Inflammopharmacology.2009;17(5); 267–274.
30. Gosslaua, A.,Chenb K., Hoc C.T., and Li S.Anti-inflammatory effects of characterized orange peel extracts enriched with bioactive polymethoxyflavones. Food Science and Human Wellness.2014;3;26–35.
31. Hasan türkez. The protective effect of boric acid on aluminum-induced hepatotoxicity and genotoxicity in rats.Turk J Biol. 2011;293-301.
32. Claudia Preckel.Cinnabar, Calomel and the Art of kushtasāzī, Mercurial Preparations in Unani Medicine ASIA. 2015; 69(4); 901–932
33. Joe,B, Vijayakumar,M., Lokesh, B.R.,. Biological properties of curcumin-cellular and molecular mechanism of action.Crit.Rev.Food Sci.Nutr. 2004;44;97-111
34. Shanmugapriya P, Murugesan M.Toxicological Profiling Of SanthaSanthrodhayaMathirai (SSM) A Siddha Herbomineral Formulation in Rats. IOSR Journal of Dental and Medical Sciences. 2016; 15(4); 01-08.
35. Nielsen FH, Hunt CD, Mullen LM, et al.Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women.Faseb J .1987;1;394–397.
36. Ince S, Kucukkurt I, Cigerci I.H, et al.The effects of dietary boric acid and borax supplementation on lipid peroxidation, antioxidant activity, and DNA damage in rats. J Trace Elem Med Biol.2010; 24;161–164.
37. Turkez H, Geyikoglu F, Tatar A, et al.Effects of some boron compounds on peripheral human blood. Z Naturforsch. 2007;62; 889–896.
38. Zafar, H. & Ali, S, Boron inhibits the proliferating cell nuclear antigen index, molybdenum containing proteins and ameliorates oxidative stress in hepatocellular carcinoma. Arch. Biochem. Biophys.2013; 529(2);66-74.
39. Joseph R. Landolph ,Cytotoxicity and negligible genotoxicity of borax and borax ores to cultured mammalian cells. American Journal of Industrial Medicine.1985;7(1); 31–43.
40. HasanTürkez, FatimeGeyikoğlu, SuatÇolak,The protective effect of boric acid on aluminum-induced hepatotoxicity and genotoxicity in rats. Turk J Biol.2011; 293-301.
41. Sarkar PK, Prajapati PK, Shukla VJ, Ravishankar B. Evaluation of processed borax as antidote for aconite poisoning. J Ethnopharmacol. 2017 Jun 9;205:138-146.
42. Garrison FH.An Introduction to the History of Medicine.4th edition.Philadelphia; WB Saunders Co.; 1929.
43. Singer C, Underwood EA.AShort History of Medicine.2nd edition.Oxford; Oxford at the Clarendon Press; 1962.
44. Thanigavelan, V. et al., Physicochemical characterization for the quality assessment of a Siddha herbomineral pill – Karpoorachindhamanimathirai. Journal of Applied Pharmaceutical Science. 2013; 3 (03); 133-138.
45. Robert B. Saper, Heavy Metal Content of Ayurvedic Herbal Medicine Products.JAMA. December 15,2004; 292(23).
46. Robert B. Saper. Lead, Mercury, and Arsenic in US- and Indian-Manufactured Ayurvedic MedicinesSold via the Internet. JAMA. August 27,2008; 300(8); 915–923.
47. Anoop Austin .Chemical Characterization of a Gold and Mercury based Siddha Sasthric Preparation-Poorna chandrodayam .American Journal of Drug Discovery and Development.2012;1-14.
48. Savrikar, S.S. and Ravishankar B. Introduction to ‘rasashaastra’- the iatrochemistry of ayurveda. Afr J Tradit Complement Altern Med. 2011; 8(S);66-82.
49. Sathya T, Murthy B & Vardhini N.Genotoxicity evaluation of certain Bhasmas using Micronucleus and Comet assays. TheInternet Journal of Alternative Medicine.2009;7(1).
50. Arunachalam J. Researches on mercurial preparations: The prime requirement for their acceptance in medical world. Ayu. Apr-Jun 2015; 36(2); 118–124.
51. Wylly ramses et al. Protective effect of curcumin against heavy metals –induced liver damage. Food and chemical toxicology. 2014; 182-201.

*****