2. Literature review

2.1. Shodhana

A. Ayurvedic system of shodhana

Rasa shasthra explains processing of drugs under the name “Samskara”, which is capable of modifying the qualities of the drug. Shodhana is one such process used for Samskarana of drugs. The term “shodhana” in Sanskrit means purification. However the word Shodhana is being used with a broader perspective in Rasa-shastra. Therefore in Rasa-shastra the shodhana means a process of not only purification but also involves the detoxification and enhancing the efficacy of the drugs. The poison or toxins of the plant/ part of the plant will be converted to safe, effective and life saving medicine by subjecting them to the process of shodhana [1-3].

Shodhana processes are used to remove visha (toxic compounds) or decrease concentration of toxic constituents or convert them to chemically modified compounds which are less toxic and/may be more potent.

There are claims that herbal drugs when given after shodhana process possess lesser toxicity and enhanced efficacy. The data on scientific validation of shodhana processes is scanty.

It is clear from the ancient literature that a single shodhana process is not described for all the drugs or more than one process is described for a single drug. However, the shodhana process described for various drugs differs depending on the Guna (nature) and Dharma (properties) of the drug [1].
Various shodhana processes include

1. Simple washing with water, lime-water.
2. Triturating (mardana) with borax.
3. Swedana (heat treatment with liquids)
4. Treating with cow urine
5. Treating (boiling with) cow milk/goat milk
6. Frying with cow ghee.

In addition to these, there are several other processes and/or, combination of any two or more above mentioned processes are described in the texts.

Objectives of Shodhana

* To increase the brittleness
* To prepare herbo-mineral preparations
* To reduce toxicity
* To enhance safety
* To enhance potency
* To produce synergistic effect with other plant preparations as herbal formulation [1-6].
B. Scientific reports on impact of shodhana on phytochemical and pharmacological profiles of various herbs & mineral preparations

i. Aconite

The toxicity of aconite is decreased by treating it with cow urine and boiling with cow milk. Upon shodhana process with cow urine, the total alkaloid content is decreased. Treatment with cow urine increased the contents of aconitine, hypoaconine and benzylhypoaconitine and reduced the concentration of mesaconitine, benzylaconitine and benzylmesaconine. This indicates that shodhana process with cow urine and boiling with cow milk has removed some alkaloid constituents and also induced some hydrolitic changes [7].

ii. Croton tiglilum (Jayapala)

Croton seeds were subjected to swedana with cow’s milk by using dola yantra for three hours, after removing its raphae and apply Bhavana (trituration) treatment with lemon juice. The phoral content of the croton oil was reduced significantly due to swedana process. It is also reported that the toxicity is reduced and pharmacological potency is increased [8].

iii. Mercury

Asthā samskaras (8 methods of purification) for mercury are being prescribed namely: Swedana (boiling with cow’s milk in dola yantra for 3 h), Mardana (trituration), Murchchhana (trituration with Aloe vera for removal of mala (extretory materials), triphala for removal of vahni and with Chitraka for removal of visha. Trituration
was continued till the liquid nature is lost. It is said that this converts mercury dosha-mukta (free from poisonous nature), Uttapana (recovery of mercury with the help of sunlight, heat etc. It removes the unwanted results of Murchchhana), Patana (distillation of mercury), Rodhan (immersion of product from patana in salt water for 3 days), Niyamana (steam heating) and Dipana (steaming with metals, minerals and plant products. This gives rasa form i.e. consumable form) [1-5].

iv. Nux-vomica

Ancient literature prescribes more than one shodhana process for detoxification of the *Strychnos nuxvomica*. Few types of shodhana processes described here:

1. Nux-vomica seeds shall be soaked in gomutra (cow urine) for 7 nights; fresh gomutra is to be replaced every night. There after, it is removed and washed with water. Then seeds shall be further detoxified by Swedhana (boiling with godugdha (cow milk) in dolayantra for 3 h). The seed coat and embryo are removed. The cotyledon shall be roasted in cow ghee and powdered well.

2. The seeds are fried in cow ghee by slow heating, and then the seeds are finely powdered and used.

3. The seeds are soaked in cow’s milk and subjected to swedana in dola yantra for three hours (one yama). Then the seeds cleaned with water, seed coat & embryo are removed, then dried and powdered [1].
In addition to the ancient literature several native practitioners also adopting slightly modified shodhana process for detoxification of seeds of nux-vomica. One such shodhana process adopted by a native practitioner of Shimoga by name Shree Raghavendra is herewith explained. The seeds of nux-vomica are soaked in cow urine for seven nights and changing the urine every night. Thus obtained seeds were soaked in cow milk for three days. Finally the seed coat and embryo were removed and fried with cow ghee. In this method heat treatment in the second step is replaced by soaking seeds in cow milk for 3 days.

It is reported that the alkaloid content was decreased upon shodhana process [9]. However, there are no scientific reports on the rationale and validity of this process in detoxification of nux-vomica.

**Advantages of shodhana process on nux-vomica seeds**

1. Shodhana process eliminates the irritant trichomes so that the powder drug can be easily swallowed.
2. It is easy to make seed powder.
3. There are claims in ancient literature that the seed products after shodhana are less toxic and more efficacious.

Therefore powdered seeds of nux-vomica after shodhana is used in Ayurveda for treating various ailments including analgesic, anti-inflammatory, arthritis, ulcers, gastric troubles, nerve tonic, aphrodisiac, liver diseases, anti-obese, anticancer, stimulates cardiac, respiratory centers in brain etc. since the ages [1-5].
**Chinese system of detoxification on nuxvomica seeds**

The seeds (10G) were roasted with sea sand (10G) until the seeds became dark yellow color. Then the seeds were boiled in water for 10 min. and then dried thoroughly. The dried seed materials were parched with sesame oil turning to a pale yellow. The Chinese method claims that the detoxified seeds are highly potent and can be used safely [10].

**Influence of detoxification on phytochemical & pharmacological profiles of seeds of nux-vomica**

1) According to the Chinese system of detoxification, heat treatment of the seeds reduced the normal levels of the principal alkaloids strychnine; brucine and the amounts of isostrychnine, isobrucine, strychnine-N-oxide and brucine N-oxide are increased. The toxic strychnine and brucine alkaloids were transformed into their isoforms and N-oxide derivatives after detoxification. The reports are indicating that these derivatives of principal alkaloids are less toxic and more potent [11, 12].

2) Processing of nux-vomica seeds with sand bath and other Chinese traditional methods reduced the toxicity of the seeds and enhanced the safety of the seeds [13, 14].

3) There are reports that loganic acid, the known toxic substances present in the seeds, is reduced after subjecting them to Chinese method of detoxification [15].

4) Strychnine content in detoxified seeds was reduced to one tenth of unprocessed seeds of Nux-vomica [16].
v. Guggul

Though guggul is not classified as visha or upavisha, it is subjected to shodhana process to reduce side effects and to potentiate the efficacy of preparations. In ancient literature there are three methods prescribed for detoxification of guggul [1-3].

They are -

1. Guggul is boiled with cow milk for three hours (Swedana)
2. Guggulu is boiled with aqueous extract of triphala (Amalaki, Haritaki, Bibhitaki and Pippali) for three hours
3. Guggul is boiled with cow urine for three hours

Ancient literature clearly explains the role of each ingredient used in the shodhana of guggulu (Swedana with triphala) as follows:

**Amalaki:** *Emblica officinalis* (enhances the activity of formulation)

**Haritaki:** *Terminalia chebula* (enhances the activity of formulation)

**Bibhitaki:** *Terminalia belerica* (enhances the activity of formulation)

**Pippali:** *Piper longum* (enhances the activity & enhances the bioavailability of the formulation)

**Potentiator** - The triphala kashaya, because of its vrana shodhana (would healing) vedanasthapana (Analgesic and anti-inflammatory) properties, enhance the therapeutic efficacy of formulation.
**Antidote**- Guggul is being a resin does not dissolve in the system easily. In large doses of guggul can cause constipation, burning sensation in the urine, eyes etc. It is reduced by swedana with thriphala, which is a mild laxative and also beneficial to the eye.

**Bioavailability enhancer**- Various pharmacokinetic studies showed that pippali is a bioavailability enhancer. Thus in this formulation the pippali has been included as bioavailability enhancer [18].

**Guggul shodhana procedure**

One of the plants of the present study i.e. guggul is therapeutically used for treating various “Vatha and kapha dosha” related diseases. But the side effects associated with it limit its usage. However, in Ayurveda this oleogum resin is used after subjecting it to various shodhana processes. The ancient literature prescribes specific shodhana process for detoxification of guggulu as below

Guggul must be bundled in a strong cloth (pottali) and boiled in dolayantra containing 4 parts of gomutra (cow urine), godugdha (cow milk) or Triphala Kasaya. When all the guggul dissolves in milk/Triphala kasaya, pottali is removed and the liquid is evaporated to collect purified guggul [17, 18].

**Advantages of shodhana process on guggul**

The Ayurvedic literature claims that shoditha guggul is less toxic and more effective. Further it was indicated in the literature that bioavailability is increased [18, 19]. However, there are no scientific
studies to verify and validate such claims. Therefore in the present study it was planned to study the impact of shodhana on the physicochemical, phytochemical and pharmacological profile including toxicity of guggul.

**vi. Datura metel var. fastuosa seeds**

The entire plant of Datura is used in medicine, but its seeds are exceedingly potent as therapeutic agent and since these seeds are classified as upavisha in Ayurveda, the seeds can be used after subjecting them to shodhana [1-3].

**Adverse effects of datura seeds**

If it is used without appropriate shodhana may cause dryness of the mouth, excessive thirst, cramps, unconsciousness and giddiness. Most of these side effects are due to anticholinergic property of the alkaloids present in this plant.

**Method of shodhana of seeds of Datura metel**

The seeds were soaked in sufficient gomutra (cow urine) for 12 h. Then they are washed with water and subjected in a dolayantra (hanging the drug in liquid while boiling) containing sufficient godugdha (cow milk) for 3 h. The level of the milk must be above the level of the pottali (cloth bag) and this level must be maintained throughout the swedana process. The seeds are used after removing the seed coat.

**Dose:** 25mg-50mg. It is generally used along with cow milk in combination with other drugs in a compound form [5].
The detailed scientific data on the shodhana and its impact on the datura seeds are not available. Hence the seeds of this plant are selected for the present study.

Keeping the available literature and the claims in view, it is planned to study the impact of shodhana on the selected plants for the study namely:

01. Seeds of *Strychnus nuxvomica* Linn.

02. Oleogum resin of *Commiphora mukul* Burg.

03. Seeds of *Datura metel* var.*fastuosa* Linn.

The scientific information relevant to the study that is available in the modern literature is recorded in the next pages.
2.2. Literature review of studied plants

2.2.1 *Strychnos nux-vomica* Linn.

**Botanical classification**

Kingdom: Plantae

Subkingdom: Tracheobionta

Superdivision: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida – Dicotyledons

Subclass: Asteridae

Order: Gentianales

Family: Loganiaceae

Genus: Strychnos

Species: Nux-vomica

**Biological Source**

Nux-vomica is the dried ripe seeds of *Strychnos nux-vomica* Linn. Family: Loganiaceae.

**Names in various languages**

Hindi - Kuchala; Kannada-Kasarkana; English- Nux-vomica; Telugu-Mushini ginjalu; Bengali-Kunchila; Marathi- Kajara; Gujarati-Jherkuchala; Tamil Yettikottai; Malayalam- Kagniram.

Sanskrit: Kupilu, karaskara, Kunchavriksha, Kulaka, Vishatinduka.

English: Crow-figs, Semen strychni, nux-vomica seed

**Geographical source**

It is indigenous to east India and is largely collected from forest in Sri Lanka, Northern Australia and India. It is abundantly found in
South India i.e. in Tamil Nadu, Kerala and Malabar coast, it is also available in the forest of Bihar, Orissa, Konkan, Mysore and Gorakhpur.

**History**

It is derived from a Greek work Strychnos, meaning poisonous and nux-vomica indicates a nut with vomiting effects.

**Botanical description:** An evergreen glabrous tree, a deciduous tree sometimes reaching 30 m in height, often with short axillary spines, bark thin, grey smooth or rough with lenticles.

**Seeds:** Colour is greenish to brown, taste is intensely bitter, 10-30 mm in diameter and 4 to 6 mm in thickness, disc shaped, somewhat flat or irregularly bent and concavo-convex, margin of the seeds is rounded. Surface of the seeds is silky due to the radiantly arranged, densely covered, closely appressed unicellular lignified covering trichomes. The presence of endosperm, embryo and cotyledons can be confirmed in the L.S. of the seed.

**Leaves:** Leaves 7.5-15 by 4.5-7.5 cm, opposite, entire, ovaee, 5 nerved, broadly elliptic, acute, obtuse, or shortly acuminate, glabrous and shining, 5-nerved (the lateral pair often), base usually rounded; petioles 6-13 mm. long.

**Flowers:** Flowers numerous, greenish white, borne on terminal pubescent pendenculate, corymbose cymes. Flowers during March-April and fruits ripen during winter. Flowers usually regular, hermaphrodite, generally in 2-3-chotomous cymes, varies in size and colour. The characters of parts of flowers are calyx inferior; 2.5 mm
long, tube short; lobes usually 4-5 corolla, 1.3 cm, gamopetalous, 4-5 lobed or partite; lobes imbricate or valvate. Stamens 4-5 inserted on the corolla-tube, alternate with its lobes; anthers two-celled and Ovary free, usually two-celled; ovules one-many in each cell; styles 1 or 2.

**Fruits:** Fruit globose 2.5-7.5 cm. diameter slightly rough but shining, orange-red when ripe. Fruit capsular or indehiscent, one-many seeded. The characters of seeds are various, albuminous; embryo usually straight; cotyledons broad or narrow; radicle usually inferior.
Plate no.2.2.1.1

Photograph showing *Strychnos nux-vomica* plant
Plate no. 2.2.1.2

Photograph of *Strychnos nux-vomica* seeds

Collection and preparation

The seeds are collected from wild grown plants by local tribal community. The Nux-vomica tree is found throughout the tropical area 1300 m above the sea level. Fruits of the plants are orange yellow berries of normal size. Each fruit contains about 4-5 seeds and heavy bitter pulp. The ripened fruits are collected and seeds are freed of the pulp. They are washed with water thoroughly. Unripened seeds are separated by floating test in water. The seeds are dried on mat and packed in gunny bags for marketing. The collection of the fruit and seeds is carried out from November to February in India [6, 22, 23].
Macroscopical characters of seed

Nux-vomica seeds are extremely hard and should be boiled in water for at least an hour in order to soften them sufficiently for dissection. The seeds are greenish grey in colour; disc shaped 10-30 mm in diameter and 4-6 mm in thickness. Most of the seeds are nearly flat and regular in shape, but a few are irregularly bent and somewhat oval in outline. The edge is rounded and acute. The testa is covered with silky, closely appressed radiating hairs. In the centre of one of the flattened sides is a distinct hilum and a small prominence on the circumference, marks the position of the micropyle, which is joined to the hilum by a radiant ridge [6].

Microscopical characters of seeds

Transverse section of the seed outer part shows an epidermis with characteristic lignified trichomes. The bases of trichomes are very large, thick-walled with slit-like pits, and interlocked with each other. Trichomes upper part have about 10 longitudinal ridges, united by a thin wall, and are placed almost at right angle to the bases and radiate out towards the margin of the seed. It shows the testa with characteristic silky appearance. Epidermis is followed by collapsed parenchyma, which together with epidermis forms thin testa of seed. The endosperm is composed of cellulosic, non-lignified thick-walled cells. Endosperms cells are larger towards inside. The endosperm cells are connected by very fine protoplasmic threads, termed plasmodesma. Strychnine and brucine, and a few aleurone grains
present in endosperm cells. Strychnine is abundant in the inner part of the endosperm while brucine in the outer part [6].

The endosperm consists of large, thick walled cells, when mounted swell if the seeds have been boiled or treated with solution of potassium hydroxide the walls are non-lignified and are of carbohydrate nature since they yield galactose and mannose on hydrolysis. When mounted in a solution of iodine, they show well marked protoplasmic threads (plasmodesma) passing through the walls and an oily plasma containing a few aleurone grains and the alkaloids Strychnine and brucine. Strychnine is most abundant in the inner part of the endosperm and brucine in the outer layers. Histochemical observations can be made by mounting a section in a solution of ammonium vanadate in sulphuric acid; the violet coloration in the various parts of the section indicate the presence of strychnine and mounting the same in nitric acid gives crimson color indicating the presence of brucine [6].

**Phytochemicals** [6, 20-23]

**a. Indole alkaloids**

About 18 alkaloids were identified from the seeds. It contains 1.8-5.3 %G of total indole alkaloids, majorly strychnine and brucine. Strychnine is much more physiologically active than brucine and seeds are therefore assayed for strychnine and not for total alkaloids. They usually contain about 1.23 %G of strychnine and about 1.55 %G of brucine. Minor related alkaloids include α-colubrine, β-colubrine icajine, 3- methoxyicajine, strychnine-N-oxide, isostrychnine-N-oxide,
brucine-N-oxide, isobrucine-N-oxide, isostrychnine, isobrucine, protostrychnine, 16-Hydroxy-α-colubrine, 2-Hydroxy-3-methoxy strychnine, vomicine, novacaine, N-oxysterchnine, diaboline. Two colorless monoquaternary bisindole alkaloids were reported from the seeds. They are namely: 4-N-hydroxymethyl strychnidin-17-acetic acid and 10, 11-dimethoxy-4-N-hydroxymethyl strychnidin-17-acetic acid, N-methyl secondary pseudo β-colubrine, 4-hydroxy strychnine, 15-hydroxy strychnine.

**Fig. no 2.2.1.1 Strychnos nux-vomica phytochemicals [14]**

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<th>Name</th>
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Loganic acid
**Tannins**

The seeds also contain caffotannic acid and chlorogenic acid.

**Glycosides**

The glycosides reported from the plant are iridoid glycosides of loganic acid, 3’O-acetylloganic acid, 4’O-acetylloganic acid, 6’O-acetylloganic acid, 7’-O-acetylloganic acid. Loganin and secologanin content in fruits including both pulp and seeds is about 5%. These compounds are intermediate in the biogenesis of the strychnine type alkaloid and reported to contribute significantly for the toxicity of the seeds.

**Fixed oil**

The seeds contain 3 %G of fixed oil (both saturated and unsaturated fatty acids are present). β-sitosterol and stigmasterol, oleanolic acid and its 3β-acetate and a saponin containing oleanolic acid.

**Sugars**

Galactose and mannose are reported to be present in seeds.

**Fruit pulp:** Phenolic glycoside cuchiloside and salidroside are present.

**Leaves:** It contains only strychnine and brucine. Recent investigations revealed that leaves of very young plant also contain vomicine as a major constituent alkaloid along with alkaloid icajacine (n-methyl pseudo strychnine).

**Bark:** The bark contains 9.9 %G total alkaloids made up of brucine (4.8 %G), strychnine (1.58 %G) and pseudo strychnine and pseudobrucine.

**Wood:** The wood also contains strychnine and brucine.
**Roots:** The roots contain about 1 %G total alkaloids of which brucine forms 0.2 %G, strychnine 0.7 %G, 0.1 %G C-mavacarine, a quartenary alkaloid has been found in root bark. It also contains strychnocrysine, a new bisindole alkaloid.

Nux-vomica plant also contains para hydroxyl benzoic acid, vanillic acid, 2-hydroxy 4-methyl benzoic acid, sinapic, syringic acid and kaempferol and quercetin flavanoids.

**Physical properties of nux-vomica principal alkaloids**

**Strychnine:** Brilliant, colourless cubes or crystalline powder. Strychnine is very slightly soluble in water, freely soluble in nitric acid and sulphuric acid. It is freely soluble in chloroform, alcohol, benzene and pyridine. Taste is bitter, laevorotatory. Strychnine hydrochloride dehydrate is soluble (1G in 40 ml water and 1G in 80ml ethanol).

**Brucine:** Crystalline, soluble in chloroform and alcohol. It is readily distinguished from strychnine by being readily oxidised by dilute nitric acid with the formation of an intense red colour. Taste is bitter, leavorotatory; it is used as an alcohol denaturant due to its extremely bitter taste. Brucine tetrahydrate is soluble in 1.3 ml alcohol, 5ml chloroform. The pH of saturated water solution is 9.5.

**Nux-vomica as an ancient medicine**

Nux-vomica (Kuchala) seeds are extensively used in Indian system of medicine for various therapeutic purposes. According to ayurvedic texts, Kuchala saeds are said to be tikta (bitter), katu (pungent) grahi (astringent), Deepana (digestant), uttam kamodipana (powerful sex stimulant), mutral (diuretic), medohara (anti-obesae),
ugra veerya and tiksahna sara medokarak (intoxicator) and a good nerve tonic. It destroys kapha and pitta (metabolism) and prouduces mada (intoxication) in the human body. Therefore, it is advised to be used after proper purification, otherwise they produce severe toxic symptoms on the human body. In Rasa-shastra it has been included in the group Upavisaha (moderately toxic).

The fruit is bitter, acrid, pungent; heating, appetizer, tonic, astringent to bowels, antipyretic; curses leucoderma, “Vata” and “Kapha”, diseases of the blood. Fruits are used in itching, piles, ulcers, anaemia, jaundice, urinary discharges (Ayurveda). The fruit is bitter and poisonous; heating, tonic, aphrodisiac, diuretic, emmenagogue; cures pain in the joints, lumbago, ringworm, piles; useful in paralysis and weakness of the limbs (Unani) [4].

The leaves when applied as poultice, promote healing action on wounds or ulcers. It arrests any further formation of them, and those in the deeper parts perish immediately when the poultice is applied. The root-bark is ground up into a fine paste with lime juice, and made into pills that are effective in cholera [5].

In Konkan, small doses of the seeds are given with aromatics in colic, and juice of the fresh juice of the fresh wood is given in dose of a few drops in cholera and acute dysentery. In some parts of Konkan small quantities of the seeds are taken, apparently as a stimulant, or in lieu of opium. In the Indian Archipelago, the wood is used as a popular remedy for dysentery, fevers and dyspepsia. In Ceylon, the roots are ground with water and applied to the bite snake [5].
In Cambodia, the seed is used as an emetic. Internally, an infusion of the bark is given in epilepsy; externally the bark is used in the treatment of ulcers and leprosy.

Externally it alleviates pain, oedema and is used as an analgesic. It is used for external application in rheumatoid arthritis, osteoarthritis. An application of nux-vomica seeds with turmeric cures oozing and foul smelling ulcers. This paste is also effective in ulcers. The pulp of the leaves is useful in oozing ulcers.

It is useful in vata disorders like neuralgia, facial palsy, hemiplegia, insomnia. Excess dose of seeds leads to intoxication and convulsions.

Being bitter and pungent, it is a good appetizer, digestive and astringent. It is useful in abdominal pain by ushna (heat) and vata alleviating property. It is used in anorexia, gastric inflammation, colitis, piles and parasitic infection. It is the medicine of choice for gastric laxity and spasm.

Being ushna and tikshna (potentiating action), it is a cardiac stimulant and hypertensive. It alleviates oedema caused by kapha. It is useful in disorders like cardiac laxity.

Being pungent and bitter, it is kaphahara (alleviates cough). It is also useful in the treatment of inflammation of lungs.

It is an excellent rasayan. It cures laxity of body tissue. It is a good medicine for the elderly, complaining of loss of appetite, insomnia and laxity of body (Satmikaran). Nux-vomica is useful in
dermatoses, pyrites and excess perspiration. Nux-vomica is effective in fever with shivering and periodical fever [4, 5].

Ancient Chinese system of medicine adopted nuxvomica containing preparation in the treatment of nervous diseases, vomiting, arthritis and traumatic pains, etc. The seeds have been used in activating the alleviating pain, reducing swelling. Nux-vomica has been effectively used in Chinese folk medicine for the treatment of liver cancer and associated pathological abnormalities [20, 21].

**Properties and uses of purified nux-vomica**

It is bitter & pungent taste. It alleviates all the three doshas, especially Kapha and Vata.

Purified nux-vomica (seed) ground into a fine powder should be used along with milk and sugar. It has several properties as described in Ayurveda-

Rasa-Katu, tikta
Guna-Laghu
Virya-Usna
Vipaka-Katu
Karma-Kapha vata haram, visa haram, grahi
Amayika Prayoga- Kusta, Kandu, Arsa, Vrana, Vataroga etc.

**Toxic effects:** Impure nux-vomica causes delirium and paralysis. It creates symptoms like muscular spasms, opisthotonus, tremors and dilatation of the pupils. Impure or excess dose of nux-vomica causes convulsions and tentanus like symptoms. These symptoms appear
within 10 to 20 min after its oral administration and cause death by asphyxia.

**Dose:** The seeds and root bark are used. Shodhana processed powder 25-125 mg twice daily with milk/ghee/butter. It is generally used in combination with other drugs in a compound form.

**Precautions:** While taking nux-vomica, the patient should avoid heat producing diet and drinks. He should use more of cow's milk, butter and ghee. Cow ghee is an antidote for nux-vomica poisoning [3].

**Important formulations containing nux-vomica:** Agnitundi, Agnitundi rasa, Navajeeva rasa, Lakshmivilas rasa, Vishamushti, Navajeewan, Vajravati, Agnitundi vati, Våtagajankusa ras, Krimirnudgara rasa, Visatinduka tada, Visatjnduka vati, Karaskara ghrita [1-3].

**Allied drugs:** The seeds of *Strychnos wallichiana* are used as substitute to nux-vomica as their alkaloid content and composition are comparable to that of seeds of *Strychnus nuxvomica*. It contains unlignified detached trichomes. Its alkaloidal content is 2.5% to 3% of which 60% is strychnine. The seeds are used for the isolation of strychnine.

Ignatius beans are the seeds of *Strychnos ignatti*, a plant found in Phillipines as well as Vietnam and elsewhere. The fruits are larger than those of nux-vomica and may contain as many as 30 seeds. They are about 25mm long, dark grey in colour and irregularly ovoid in shape. The structure closely resembles that of nux-vomica, but the testa, which bears irregularly arranged greyish hairs, is easily rubbed
off and is almost entirely absent in the commercial drug. The seeds contain about 2.5 to 3.0 %G of alkaloids of which about 46 to 62 %G is strychnine and brucine.

The seeds of S. ignatii from Java (S.tieute) contain 1.5 %G strychnine; lack of brucine and from Hainan (S. hainanensis) contains mainly brucine with little strychnine. Those of S. lucide (S. ligustrina) from Australia contain predominantly brucine with a varying proportion of strychnine [6, 22, 23].

**Adulterants**

The dried seeds of *Strychnos nux-blanda* Hill are used as adulterant to nuxvomica seeds. These are similar in size, pale in colour with a distinct ridge on the edge of the seeds. Nux-blanda seeds are regular in shape and contain traces of alkaloids.

The dried seeds of *Strychnos potatorum* are another adulterant to authentic drug. The seeds are also known as clearing nuts. They are smaller and thicker with yellowish-buff colour. Seeds contain diaboline, traces of strychnine and brucine [6].

**Therapeutic uses**

The action of the whole drug closely resembles that of strychnine. The alkaloid was formerly used as a circulatory stimulant in surgical shock, but its use is now more limited and used as a respiratory stimulant in certain cases of poisoning. Like other bitters, strychnine improves the appetite and digestion, but it has been considerably
abused as a general tonic. Due to its bitter taste, nux-vomica is used as bitter stomachic and tonic.

It is the central nervous system stimulant. It increases the blood pressure and is recommended in certain forms of cardiac failure. It stimulates respiratory and cardio-vascular systems. Brucine possesses very less physiological actions and is about one sixth in potency as compared to strychnine. However, it is four times bitter than strychnine. Brucine is used for denaturing alcohol and in edible fats as a standard for bitterness and as dog poisons [6].

Strychnine is mainly the central nervous system stimulant and is a spinal poison. The main effects of strychnine are on the CNS particularly on spinal cord leading to the production of convulsions. Strychnine showed remarkable negative chronotropic activity on frog isolated heart and guinea pig atria. It retained its activity in vivo also (open chest dog model). Strychnine (50mg/kg) when injected subcutaneously increased the levels of acetylcholine in spinal cord and sustained the convulsions in frog for 4 h [21-23].

**Scientific reports on nux-vomica**

It is indicated in the literature review of seeds of nux-vomica that the Chinese traditional detoxification method removed the fine hairs that could cause throat irritation and changed the intrinsic alkaloids such as brucine and strychnine into their N-oxidative derivatives which are less toxic [20, 21]. It was also reported that the alkaloids in crude and processed Semen Strychni had the different
pharmacological and toxic effects. For example, brucine in crude nux-vomica was claimed to be a morphine-like activity (analgesic activity), whereas its derivative or brucine N-oxide existing in sand-processed nux-vomica was more of a NSAIDs-like properties. Brucine act more morphine like analgesic drug, while brucine-N-oxide acts like a NSAID via the inhibition of synthesis of release of prostaglandins. The COX & MAO activities inhibition might be involved in the antinociceptive and anti-inflammatory activities of brucine and brucine N-oxide. Brucine N-oxide exhibits potent anti-inflammatory activity when compared to brucine substantiating the use of processed seeds of nux-vomica rather than crude nux-vomica in the treatment of diseases associated with pain and inflammation [24].

It is reported that nux-vomica possesses allergen-specific IgE antibody response suppressive property and suggests its possible application in allergic conditions [25].

It was demonstrated that the leaves of *Strychnos nux-vomica*, an important plant in traditional medicine, possess both non-enzymatic and enzymatic antioxidant principles [26].

Further, the seeds of *Strychnos nux-vomica* have been used in the traditional medicine as a folk remedy for the treatment of cancer. It is due to the arrest of G2/M cell cycle involving multiple signaling pathways resulting in apoptosis of gastric carcinoma AGS cells by ethanolic extract of seeds of nux-vomica [27].
Brucine, strychnine and isostrychnine possess significant inhibitory effects against HepG2 cell proliferation, whereas brucine N-oxide not possessed such effect. Brucine might be a promising NSAID, which was effective in the reatment of liver cancer associated with pain and inflammation. It was reported that seeds of Strychnos nux-vomica are effective against HepG2 cells proliferation, among which brucine cause HepG2 cell death via apoptosis, probably through the participation of caspase-3 and cyclooxygenase-2 [28].

Alkaloids of nux-vomican significantly inhibit the proliferation of adult rat neuroprogenitor cells and these effects are probably selective, suggesting the potential of nux-vomica alkaloids as new drug for treatment of neurocytoma [29].

Strychnus nux-vomica was reported to possess anti-proliferative and cytotoxic effects on human multiple myeloma cell line - RPMI 8226 and it was attributed to the strychnine and brucine content of it [30].

It was also reported that the cytotoxicity induced by brucine from the seeds of Strychnos nux-vomica is due to apoptosis, and it is mediated by cyclooxygenase 2 and caspase 3 in SMMC 7221 cell lines [31].

The methanolic extract of nux-vomica was reported to possess in vivo hypouricaemic activity against potassium oxonate-induced hyperuricaemia in mice. It is due to the inhibitory effects on xanthine
oxidase [32]. Furthermore, it was demonstrated that the ethanolic extract of nuxvomica possess anti-snake venom activity [33].

Methanolic extract of nux-vomica effectively inhibit diarrhea induced by castor-oil in mice [34].

Though several reports are available on the pharmacological, toxicological properties of seeds of nux-vomica and its constituents, there is a paucity of information on the influence of shodhana on them.

The literature on the guggul and datura (other two herbs of the study) are recorded in the following pages.
2.2.2 *Commiphora mukul* Engl. (guggul)

**Botanical classification**

Kingdom: Plantae

Subkingdom: Tracheobionta

Superdivision: Spermatophyta

Division: Magnoliophyta

Class: Eudicots

Subclass: Rosids

Order: Sapindales

Family: Burseraceae

Genus: Commiphora

Species: mukul or wightii

**Botanical sources:** Guggul is oleogum-resin obtained by incision of the bark of *Comiphora mukul* (H. & S.) Engl, *Commiphora wightii* (Arn.), Bhand. This is even called by *Balsamodendron mukul*

Family: Burseraceae.

**Synonyms**

Sanskrit: Guggulu, Guggula, Gugala, Gugguloo, Devadhoop, Dhoorta,

Koushika, Pura, Pulankasha.

Guggulu- Protects from all the diseases

Devdhoop- It is used in incense products to worship God

Kaushika- originates from inside of the plant

Pura- best among all the medicinal plants

Pulankasha- scrapes out the unnecessary fat from the body
**English**: Indian bedellium

**Canarese**: Guggulu, guggul, Guggal, Ranghan turb, makal, Guggal.

**Hindi**: Gugala, Guggal, Guggul, Guggulu, Gugava, Gugavik, Mukul, Ranghanturb, Gogil, Bhansagugul.

**Kannada**: Kanthgal, Kangah, Guggul, Invadol-Guggala.

**Telugu**: Meshakshi, Gukkal, Guggal, Gugal, Gukkula, Maishakshim, Mahishaksh-Gugilamu, Cheetu Mahishashi,

**Parts used**: Gum resin
Plate no 2.2.2.1
Photograph showing *Commiphora mukul* plant

Plate no 2.2.2.2
Photograph showing guggul oleo-gum-resin
**Collection:** *Commiphora mukul* is a small thorny tree with slightly ascending branches, which are 4 – 6 feet tall. The plants are usually planted in hedges. The tree remains without any foliage throughout the year. The bark is ass coloured and comes off periodically as rough flakes, exposing the inner surface of the bark, which also peels off. It exudes a yellowish balsamic odoured resin known as gum guggul. It is collected in cold season and the yield is about one kilogram of the oleo-gum resin.

**Characters:** Guggul occurs as viscid, brown tears; or in fragment pieces, mixed with stem, piece of bark; golden yellow to brown in color. With water it forms a milk emulsion. It has a balsamic odour and taste is bitter, aromatic.

**Botanical description of the plant:** It is a small tree or shrub with spinescent branches. It is woody shrub to small tree, branches spiny, ascending.

**Leaves:** Unifoliate, alternate or crowded at the end of short branches, cuneate-ovate, rhomboidal or oval, acute, deeply serrate, smooth and shining, leaves 1-3 foliate: leaflets sessile to sub sessile, terminal ones the largest, rhomboid to ovate in shape, irregularly toothed in margin.

**Flowers:** Small, sub sessile, 2-3 together, unisexual. Female flowers with ovary short and barren; male flowers with short stamens and imperfect anthers. Calyx is cylindrical. Petals 4-5, star-shaped, brownish red, trips curled back. Flower possess brownish, pinkish, unisexual calyx with glandular hairs forming cylindrical cup. The petals of the flowers are 4-5 and thrice as long as sepals. The
stamens are 8-10, stigma in conspicuously bilobed and drupe red in colour, ovate-acuminate in shape with 2-celled, rarely 4-valved.

**Fruits:** Red drupes, ovate, acuminate, separating into 2 fleshy valves, leaving the nut enveloped by a 4-cleft yellow pulp. Nuts ovoid, acute, splitting into two, each 1-celled.

**Distribution:** The mukul tree is a small, thorny plant distributed through India. The tree is met with in rocky and gravelly land types in warm and semi dried areas in India found growing on the foot hills, along the slopes of the hills, hillocks and scarecely on hill tops, usually in association with *Euphorbia niruvella, Gymnosporia montanel, Grewia populifolia and G. tiliacefolia* preferring hard rocky soil. It is distributed in Rajasthan, Gujarat, Maharashtra, Tamil Nadu, Karnataka, Assam extending to Bangladesh [19, 22, 23].

**Physico-chemical standards**

Foreign matter: not more than 4%

Total ash: not more than 5%

Acid insoluble ash: not more than 1%

Alcohol soluble extractive: not more than 27%

Water soluble extractive: not more than 53%

**Active constituents:** Oleo-gum resin of guggul contains gum (32%), essential oil (1.45%), sterols (guggulsterols I to VI, β-sitosterol, cholesterol, cembrene, α-camphorene (monocyclic diterpenes) mukulol (allyl cembrol), E-and Z-guggulsterols pregnen-3-ones, guggulsterone), sterols-composed of C21 or C27 steroids, with the major components being Z-and E-guggulsterone [19].
Guggul also contains volatile oils, gum and flavonoids (viz. quercetin and its glycosides) and ellagic acid, myricyl alcohol, aliphatic tetrols, sugars (sucrose, fructose), amino acids, cembrene, cembrene A, sesquiterpene alcohol-commiferine.

It is reported that resin fraction of guggul contains guggulsterones they are guggulgsterone-E, guggulsterone-Z, guggulsterone I-IV, cholesterol, seasamin, camphorene, mukulol, allylcembrol.

Seed oil contains linoleic, oleic, stearic and palmitic acids, sitosterol, stigmasterol, cholesterol, campesterol and α-spinasterol, gum contains guggullignans and essential oils like myrecene, dimyrecene and polymercene are also present [19-23].
Therapeutic uses

It is indicated in the literature that guggul is used in the treatment of hyperlipidemia, anticholesteremic, platelet aggregation inhibitory action and fibrinolytic action. It is also used in rheumatoid arthritis, inflammation, ischemic heart diseases, melatonin induced hypothyroidism, obesity and as Immunomodulator. Z-Guggulsterone showed good thyroid stimulating activity in rats which leads to reduction of cholesterol and serum lipids [18,19].

Purified guggulipid guggulsteroid mixture completely inhibited ADP-adrenaline-induced platelet aggregation. [20].

The oleo gum-resin (guggulu) from this plant is reported to reduce serum triglycerides and cholesterol as well as LDL and VLDL cholesterols, but elevates levels of HDL cholesterol significantly. Guggulu may potentially reduce the body weight by increasing thermo-genesis through thyroid stimulation. It inhibits platelet aggregation. Guggulu is reported to possess several pharmacological properties like astringent, anti-rheumatic, antiseptic, expectorant, aphrodisiac, demulcent and emmenagogue. It is also used in lotion preparations for external ulcers. It is used as gargle in tooth disorders, tonsillitis, pharyngitis and ulcerated throat.

Dosage

Guggul oleo-gum resin 1-3g, guggul lipids 300-500 mg, guggul dry extract 150-300 mg, guggulsterones 20-25 mg.


**Adulterants**

The Indian adulterants used commonly are gum resin, *Boswellia serrata* and *Hymendictyan ex cesum*. Both the species occur in arid zones along the hilly ranges. However, adulteration of gum resin of *Boswellia serrata* is common in Indian market. The colour and smell of both the gum resins after solidification almost resemble each other, since both the plants belong to the same family - Burseraceae.

There are two other species of Commiphora, *C.roxburghii* (Arn.) Engl, *C. opobalsamum* (Linn.) Engl, which also yield about 1½ - 2 lbs of gum guggul that, is collected in cold season. The gum resin is often adulterated with the resins obtained from similar resin yielding plants.

The other known adultrants are *Commiphora myrrha* (Nees) Engl. *C. abyssinica* Engl. and *C. Sehimpers* Engl [4-6, 22, 23].

**Ayurvedic profile of guggul** [1-3, 18]

**Ayurvedic properties of guggul**

Rasa (Taste)- Tikta (Bitter); Katu (Pungent)

Guna (Characteristics)- For one year old Guggulu- Laghu (Light), Ruksha (Rough), Teekshna (Sharp), Vishada (Clear), Sara (Mobile), Sugandhi (Pleasant odor)

For freshly procured Guggulu: Snigdha (Unctuous), Pichchhila (Sticky)

Veerya (Potency) - Ushna (Warm)

Vipaka (Post digestion effect) - Katu (Pungent)
Prabhava (Special action for which there is no explanation how it works) - Tridoshhara (Pacifies all the three bio humors i.e. vata, pitta & kapha).

Identification of original guggul

The original guggul is easily soluble in water making it milky white, burns on fire, melts when heated and is free from soil particles.

Ayurvedic uses

Guggulu is well known plant for its cholesterol lowering action. In Ayurveda, it is mainly used to scrap out the toxic substances, which aggravate Vata causing arthritis like conditions.

Guggul has been mentioned in the Atharvanaveda, Charaka and Sushruta Samhitas and in many Ayurvedic dictionaries. Sushruta described the etio-pathogenesis of obesity and he explained about the importance of guggul in the treatment of obesity. It is bitter, hot, acrid; laxative, stomachic, aphrodisiac, tonic, anthelmintic; causes biliousness; heals fractures, ulcers, fistula, piles; removes “kapha” (biological secretions), “vata” (nervous system), cures indigestion, urinary tract disorders, leucoderma, tumours, inflammation, tubercular glands in the neck, useful in ascites, asthma, and troubles of the chest; removes bad discharges from the ear.

Guggul is very much used in Indian system of medicine as an astringent, antiseptic, expectorant, demulcent, carminative, anti-spasmodic, emmenagogue and used in rheumatism. When administered internally it shows diaphoretic, ecologic, anti-
suppurative. The solution of gum is used as gargle for a spongy gums, chronic tonsillitis and caries teeth.

It is used as external application for reducing inflammation, pain and used in wound healing. Paste of guggul is locally applied in rheumatoid arthritis, cervical lymphadenitis, skin diseases, piles etc.

It is used as analgesic, nervine tonic, and hence guggul is useful in neuralgia, rheumatoid arthritis, sciatica, facial paralysis, hemiplegia and gout etc. It is well known and popular medicine for vata (neurological) disorders. Triphala guggul is a popular medicine given internally for wound healing.

It is an appetizer and laxative. It is liver stimulant, antihaemorrhoidal and anthelmintic due to bitter and ushna gunas (hot property). Hence guggul is useful in anorexia, constipation, liver diseases, piles and expulsion of worms.

It can act as cardiotonic. It increases haemoglobin, leucocyte count and enhances blood quality. It is useful in chronic cough and chronic asthma. It is claimed to be lithotryptic due to the property of dissolving kidney stones as well as diuretic properties. It is also useful in dysuria and gonorrhoea. Because of its ushna (heat producing), tikshna properties, guggul increases sexual power and acts as an emmenagogue. It is also useful in oligosperma, impotency, dysmenorrhoea, leucorrhoea and other gynaecological diseases including infertility. Guggul works on all tissues of body and is effective in rejuvenating body tissues and increasing strength. Fresh guggul is useful in weakness and loss of weight, but on becoming old,
it is useful in diabetes and obesity. It is also a good rasayana in obesity and diseases of vata-kapha. It also claimed to help in digestion of oil and ghee. Effective in dermatoses, enhances complexion and useful in many skin diseases. Sheetaprashamak (reduction of chills and cold) due to its ushna property and its vapours are useful in the treatment of typhoid [4, 5 and 21].

**Purification (shodhana) of guggul**

The following steps are used for the purification.

1. Sand, stone, glass etc., are removed.
2. Then it is broken into small pieces.
3. Later it is wrapped in a piece of cloth, tied and boiled with any one of the following fluids:
   a. Gomutra (cow urine)
   b. Triphala kashaya (*Emblica officinalis, Terminalia chebula* and *Terminalia belerica* fruits aqueous extract)
   c. Godugdha (cow milk)

   The boiling is continued till the guggul becomes a soft mass. The obtained soft mass is again fried with ghee and ground in a stone mortar. The purified guggul is also prepared by boiling with either of the above mentioned liquids till the whole guggul is dissolved. Then the liquid is evaporated and collected the residue and called as sodhita (purified) guggul.
Actions of guggul according to Ayurveda

_Bruhamna_ (freshly procured guggul)- Increases the bulk of body

_Vrishya_- Increases sexual potency

_Atilekhana_ (for one year old guggul) - Effectively removes unnecessary fat and toxins of the body

_Bhagnasandhana krit_- Used in the treatment of fractures

_Swarya_- Promotes the voice

_Rasayana_- Rejuvenates the body

_Deepana_- It is a good appetite stimulant

_Balya_- Increases strength of body

_Medo-anilhara_- removes unwanted fat & air of the body

**Medicinal values of guggul**

Cholesterol: It maintains normal cholesterol level and prevents from accumulation because of its _Lekhana_ guna (scraping action)

Heart: It prevents the deposition of cholesterol plaque in the lumen of the coronary arteries.

Management of weight: It supports to maintain normal body weight by not allowing the unnecessary fat deposition.

External applications :Osteoarthritis, rheumatoid arthritis, hemorrhoids, and benign tumors.

Nervous system: In the treatment of neuralgia, facial paralysis, sciatica, hemiplegia, osteoarthritis, rheumatoid arthritis.

Digestive system: anorexia, worm infestations, flatulence, liver disorders, hemorrhoids.
Urinary system: Painful urination, pus discharge in urine, renal stones.

Reproductive system: Dysmenorrhoea, infertility.

Skin: In all types of inflammatory conditions of skin like itching, pigment disorders etc.

**Some useful combinations/formulations of guggul**

Yogaraja guggulu; Kaishora guggulu; Chandraprabha vati; Simhanada guggulu; Kanchanara guggulu; Lakshadi guggulu; Pushkara guggulu; Triphala guggulu; Tryodashanga guggulu; Shatawari guggulu; Panchatiktaghruta guggulu; Gokshuraadi guggul; Arogyavardhini Rasa, Navaka Guggulu, Amrtâdi guggulu, Guggulu Tikta Kasaya Kaisora; guggul.

**Scientific reports on guggul in modern literature**

The active ingredient steroid guggulsterone, acts as an antagonist of the farnesoid X receptor and it is demonstrated to decrease cholesterol synthesis in the liver. It is reported to reduce the level of cholesterol and body weight. Oleo-gum resin of *C.wightii* was proved to be a potent hypocholesterolemic, hypo-lipidaemic, antiatherosclerotic both in clinical as well as in experimental studies [35].

It was reported that guggul treatment for a period of 8 weeks reduced the cholesterol levels in hypercholesterolemic rabbits. It was further demonstrated that regression in serum cholesterol was significantly greater in the hypercholesteremic animals than in normal animals [19].
In one more study, it was reported that 22 patients of either sex suffering from various diseases such as hemiplegia, diabetes, hypertension, ischaemic heart disease, when treated with 6-12 G of crude guggul for 15 days to one month showed a significant fall in serum cholesterol [36].

Oral administration of guggul as well as the alcohol soluble and insoluble fractions caused a fall in serum cholesterol and serum turbidity. It was even reported that among the petroleum ether fractions A, B and C of guggul, fraction ‘A’ was the most potent in increasing the regression of experimental hypercholesterolaemia in cholesterol fed chickens [37].

It was reported that, 95% alcohol extract of guggul when given orally to Indian domestic pigs kept on standard atherogenic diet over a period of six weeks, effectively reduced the total cholesterol and also serum β-lipoprotein fraction including its cholesterol and significantly altered the β-lipoprotein [38].

A steroidal compound isolated from the guggul petroleum ether extract possessed significant anti-inflammatory activity in rats. The steroidal fraction of petroleum ether had a significant effect on the primary as well as the secondary inflammation induced by Freud’s adjuvant, the activity being less than that of hydrocortisone acetate in primary inflammation; however it was more effective than hydrocortisone in reducing the intensity of secondary lesions [39].
Further, in another study showed that the steroidal component of fraction A had proved antiarthritis effect and it is superior to phenyl-butazone and hydrocortisone [40].

There is a report that oleoresin of guggul possesses antifertility effect by reducing the weight of rat uterus, ovaries and cervix with a concomitant increase in their glycogen and sialic acid levels [41].

Guggul triterpenes like myrrhanol A and myrrhanone A of C.mukul exhibited potent anti-inflammatory effect on exudative pouch fluid, angiogenesis and granuloma weights in adjuvant-induced air pouch granuloma of mice [42].

C.mukul and guggulsterone & lipid lowering petroleum ether fraction significantly inhibited LDL oxidation. The combination of antioxidant and lipid-lowering properties was highly beneficial in the treatment of atherogenesis [43].

The essential oil, chloroform extract & seven sesquiterpenoid isolated compounds from the oleo-gum resin of Commiphora mukul showed a wide range of inhibiting activity against both Gram (+) and Gram (-) bacteria [44].

Guggulsterones reported to enhance efficacy of head and neck cancer therapies by inhibition of signal transducer and activator of transcription-3 [45].

It was also reported that the guggulsterone has both hypoglycemic and hypolipidemic effects which can help to cure type II diabetes [46].
Guggulsterones reported to prevent and ameliorate T cell induced colitis and inflammation. The data suggests that, guggulsterones useful in the treatment of chronic inflammatory diseases [47].

Guggulsterone produced comparable potency against oxidative stress induced by H2O2 in PC12 cells and it is comparable to that of vitamin E. It is reported that guggulsterone attenuated H2O2-induced cytotoxicity, extracellular accumulation of LDH and NO, intracellular accumulation of ROS and Ca2+, loss of MMP and apoptosis, which may represent the cellular mechanisms for its neuroprotective action [48].

Further, it is also reported that hydroalcoholic extract of C. mukul significantly improved the cardiac function and prevented myocardial ischemia. In addition to this, guggul treatment produced a significant increase in lactate dehydrogenase levels and inhibited the reduction of protein content in heart. It was demonstrated that guggulsterones was responsible for most of the therapeutic properties of the plant with respect to cardioprotective activity against cardiac dysfunction in isoproterenol-induced ischemic rats [49].

Inspite of abundant literature available on pharmacology and phytochemistry of guggul, there is no information on the shodhana and its impact on guggul. Hence, this herbal product is selected for the present study to analyse the influence of ancient method of shodhana on phytochemistry & pharmacology of guggul.
**Triphala (three fruits)**

As per the ancient literature, one of the shodhana processes for detoxification/potentiation of guggul is “Swedana of guggul” in aqueous extract of triphala kashaya. Therefore it is hypothesized that some of the phytoconstituents of triphala might be diffused during shodhana and contributes to the potency of shodhita (detoxified) guggul. Hence, the literature available on triphala is recorded as below.

Triphala contains following fruits without their seeds along with bioavailability enhancer i.e. long pepper

**Amalaki:** *Emblica officinalis* [23]

**Haritaki:** *Terminalia chebula* [23]

**Bibhitaki:** *Terminalia belerica* [23]

**Pippali (long pepper):** *Piper longum* [23]

The above fruits were used to potentiate, enhance bioavailability of the formulation and enhance the easy digestion of guggul.
Profiles of triphala plants

Amla

Synonyms: Amlaki, Indian goose berry, Embica.

Biological sources: It consists of dried, as well as fresh fruits of the plant _Emblica officinalis_ Gaerth (_Phyllanthus emblica_ Linn) belongs to family Euphorbiaceae.

Morphological characters

Colour: green change to light yellow or brick red when matured.

Taste: sore and astringent

Size: 1.5 to 2.5 cm diameter

Shape: globose and depressed

Extra features: Fruits - fleshy obscurely 4 lobed with 6-trygonus seeds. They are very hard smooth in appearance.

Phytochemicals

a. Amla is a rich natural source of vitamin C (Ascorbic acid) and contains 600-750 mg per 100 G of the fruit pulp.

b. Tannins: Gallic acid, trigalloyl glucose, ellagic acid, phyllembline/phylemblic acid, terchebin, corilagin, emblicol. Alkaloids phyllanthine, phyllantidine present along with pectin, essential minerals iron, phosphorous, calcium present. The amla fruits are dehydrated and stored. It is found that vitamin content of
dried amla fruits is not lost considerably. It may be due to the presence of poluphenols-tannins, which retards oxidation of vitamin C.

Uses:
Amla fruits are extensively used in Indian medicine. It is used as an acrid, refrigent and also as diuretic and laxative. Dried fruits are given in diarrhea & dysentery. They are also administered in jaundice, dyspepsia and anaemia along with iron preparations. It is a popular ingredient of Triphala and Chyawanprash (anti-ageing, increase immunity) Ayurvedic formulations. It is being a rich source of vitamin C is considered important to slow the ageing process.

**Myrobalan**

Synonyms: Haritaki, Chebulic myrobalan

Biological sources: It is obtained from the dried, ripe and fully matured fruits of *Terminalia chebula* Retzr belongs to family Combretaceae.

Morphological characters:

Colour: Yellowish-brown

Taste: Astringent, slightly bitter and sweet

Size: 20 - 25 mm long and 15 - 25 mm wide

Shape: Ovate and wrinkled longitudinally
Extra features: The fruits are hard and stony with single seed, light yellow (15 to 32 mm in length). The pulp of the amla fruit is non-adherent to the seed.

Phytochemicals

Tannins: Pyrogallol type (hydrolysable tannins), on hydrolysis yield chebulic acid and d-galloyl glucose. The other tannins that are present are Chebulic acid, terchebulin, chebuliagic acid, chebulinic acid, ellagic acid, gallic acid, corialaogin, 3, 6-digalloyl glucose, β-D-glucogallin.

Other phytochemicals: Glucose, Sorbin, Phosphoric acid, succinic acid, quinic acid, shikmic acid present.

During the maturation of the tree, the amount of tannin decreases, whereas the acididity of the fruits increases.

Uses: It is used as an astringent, laxative, stomachic and tonic. The laxative property of myrobalan is due to anthracene derivatives in the pericarp. It is also an anthelmintic. Fruit pulp is used to cure bleeding. It is an ingredient of ayurvedic preparation ‘Triphala’, used for treatment of variety of ailments like as laxative, coolant, diuretic etc. Myrobalan is also used in treatment of piles and external ulcers.
**Bahera**

Synonyms: Bibhitak, Belleric myrobalan, Baheda.

Biological sources: It is obtained from dried ripe fruits of *Terminalia bellerica* Linn. belonging to family Combretaceae.

Morphological characters:

Color- dark brown to black

Taste-astringent

Size-1.3 to 2 cm in length

Shape-global and obscurely 5 angled

The fruits are pulpy with hard with stony seeds

Phytochemicals

Tannins: The fruits contain 20-30% of tannins. It contains gallic acid, ethyl gallate, galloyl glucose, ellagic acid, chebulagic acid and phyllemblin.

Cardiac glucosides: Belleric acid, belleric acid and its glucosides, arjungenine, arjunoglucosides, tomentosides.

The plant also produces gum and sugars.

Uses: It is used as an astringent and in the treatment of dyspepsia and diarrhea. It is a one of the constituent of triphala. The purgative property of half ripe fruit is due to the presence of fixed oil. The oil on
hydrolysis yields an irritant recipe. Gum is used as a demulcent and purgative.

**Long pepper**

Synonyms: Pippali large

Biological source: It consists of dried fruiting spikes of climbing vine, called as Piper longum belonging to the family Piperaceae.

Morphological characters

Colour- Pale brown to dark brown

Odour- Aromatic spicy

Taste- Hot and sweet taste

Size- 2 to 5 cm length 0.4 to 0.5 cm diameter

Shape- Circular and elongated

Spikes are cylindrical, erect and blunt

Phytochemicals

It consists of alkaloids piperine, pipertine and piplasterol (about 6%), 1% essential oil with pungent resin. Large variety contains not less than 1% of resin.
Uses

It is widely used in ayurvedic and unani medicines, especially in treatment of respiratory tract diseases. The roots are used for bronchitis, stomach-ache, diseases of spleen and tumours. It enhances appetite.

Bioavailability enhancer- Various studies have shown the effect of pippali as bioavailability enhancer. Thus in this formulation the pippali has been included as bioavailability enhancer [18].

Since all the three plants of triphala possess antioxidant principles like galloyl glucose, it is hypothesized that swedhana with thriphala kashaya (shodhana of guggul) enhances the potency of guggul. Hence, the present study is planned.

Another plant selected for the present study is dried seeds of the plant *Datura metel var fastuosa*. The literature on this study plant is recorded below.
2.2.3 *Datura metel* var.*fastuosa* Linn.

Plate no. 2.2.3.1

Photograph showing *Datura metel* var.*fastuosa* plant

Plate no. 2.2.3.2

Photograph showing *Datura metel* var.*fastuosa* flower anatomy
**Botanical classification**

Kingdom: Plantae

Subkingdom: Tracheobionta

Superdivision: Spermatophyta

Class: Magnoliopsida – Dicotyledons

Subclass: Asteridae

Division: Angiosperms

Class: Eudicots

Subclass: Asterids

Order: Solanales

Family: Solanaceae

Genus: Datura

Species: metel

Variety: fastuosa

**Biological source:** The drug is obtained from the dried whole plant of *Datura metel var. fastuosa* Linn. Family- Solanaceae

**Synonym:** Sanskrit: Unmatta, Kanaka, Kanakahvaya, Sivapriya, Māṭulaputraka, Hindi: Sada dhatura English: Thorn-apple, Angel’s trumpet, devil’s trumpet; Telugu: Ummetta; Tamil: Ummattangai/Veila-Ummathai; Bengali: Dhaturac; Gujarati & Marathi: Dhatturā; Kannada & Malayalam: Ummatta.

**Habitat and distribution**

The plant is commonly found in tropical parts of India and available even in Himalayas.
**Botanical description** [6, 23]

It is a coarse weedy annual herb, reaching over 1 m in height. Plant is pubescent.

**Leaves**: Pale green, ovate and more or less angular, unequal at the base, large, entire sinuate or toothed, bar unequal.

**Flowers**: Solitary, large, 10-15 cm long, with corolla tubular-funnel shaped, erect, whitish-purple; calyx long-tubular, 5-toothed at apex; corolla is double or triple, long-tubular to funnel-shaped, outer corolla have five and inner corolla has six to ten teeth.

**Fruit**: The fruit is about 5-6 cm long, subglobose capsule, covered with fleshy prickles.

**Seeds**: The seeds are ear shaped, flattened, numerous, closely packed, smooth and yellowish brown in colour, compressed, rugose, brown.

**Chemical constituents** [6, 23]

Datura seeds contain mainly tropane alkaloids, withanolides and fixed oil. The herb contains 0.5 %G total tropane alkaloids, among which hyoscine (Scopolamine), 1-hyoscyamine (scopoline) and atropine are present as major compounds in the plant. Hyoscine is an ester of tropic acid and scopine (tropine).

Seeds contain total alkaloids 0.23 %G and hyoscyamine 0.12 %G. Seeds also contain atropine, fastunine (mp 88 °C), fastudine (mp. 98 °C) fastusidine and fastusic acid (mp 202 °C) and withanolides like daturanolone (mp 273 °C), meteloidine, daturaolone, daturadiol. Seed oil contains oleic (64%), linoleic (18%), and saturated (16%) acids [23].
Roots contain hyoscine, norhyoscine, meteloidine, hyoscyamine, cuscohygrine and tropine. Pericarp contains β-sitosterol, scopolamine and fastusine. Fruits contain daturaolone and daturadiol.

Leaves contains scopolamine, hyoscyamine, withanolides daturametelins A-G, daturilinol, datumetine, daturilin (fresh leaves), withametelin isowithametilin, secowithametilin, withafastuosins A and B, quercetine and its glycosides, kaempferol glycosides.

Whole plant contains withanolides daturametelins A, B, & H-J [50,51], scopalamine, daturadiol, daturalone, factusine, beta-sitosterol, hyosine, hyoscyamine, fastudine, fastunine, fastusidine, fastusinine; allantoin, norhyoscyamine, daturanolone, datumetine, datumetlin, datumelin, daturilin, daturilinol, cuscohygrine, meteloidine, noratropine, tropine, pseudotropine, apoatropine, withametelin, niacin, vitamin C, apohyoscine, norhyoscine. It also contains calystegine A3, B1, B2 & B3 [56].
Fig no. 2.2.3.1 Phytochemicals of *datura metel var. fastuosa* [23, 50, 51 & 56]

(-) hyoscyamine

Datura taturin A

(-) hyoscine

Datura taturin B
withametelin B

withametelin E

withametelin F

withametelin G

withafastuosin A

withafastuosin B
Chemical test

(Vitali-Morin reaction)

1. The alkaloid is treated with fuming nitric acid, followed by evaporation to dryness (nitrated residue) and it was dissolved in acetone and added methanolic potassium hydroxide solution. If the mixture gives violet colour, indicates the presence of tropane alkaloids.

2. On addition of silver nitrate solution to solution of hyoscine hydrobromide, yellowish white precipitate is formed, which is insoluble in nitric acid, but soluble in dilute ammonia [6].

Therapeutic uses

It shows anticholinergic, delirium properties and central nervous system depressant actions due to its tropane alkaloids. It is used to reduce the secretions such as sweat, saliva and gastric juice and also to reduce spasm. It is used along with strong purgatives like senna to decrease intestinal gripping during purgation. The drug is used in cerebral excitement. It is used in the treatment of asthma and in cough. It is also used in the treatment of wounds, leprosy and tooth decay. Along with morphine, it is used as preoperative medication. Hyoscine hydrobromide is used in motion sickness, gastric or duodenal ulcers [6, 23].

Ayurvedic profile of the plant [1-5]

Five varieties of datura are mentioned in Raja Nighantu based on the colour of the flowers viz., white, violet, blue, red and yellow.
The violet flowered variety is said to be of more medicinal value. It is known in commerce as black datura. In the present study the black datura was selected.

**Shodhana (purification)**

The seeds are toxic, hence purified before the use. The seeds are boiled in cow’s milk or cow’s urine for 3 h. Then they are washed with hot water, dried and then used [1].

**Therapeutic and folk uses**

Leaf juice is applied in alopecia and inflammation. The paste prepared out of turmeric with juice of datura leaves can be used in mastitis. It is also indicated in galactorrhoea.

The seeds are beneficial in treating lice and dandruff. Intenrally it is used in treating various diseases like fever with chills, asthma, cough, pain in abdomen, diarrhea, dysentery and dermatoses. Formulations of datura seeds are used in enteric pains. Formulations like sutashekhbar are useful in pain induced by pitta (metabolism). In fever with rigors, datura seeds in curd are given before rigors start. It alleviates rigors and also post pyrexia burning sensation and body ache. Mixture of shweta (white) punarnava 1/2 tola and datura root 500 mg in cold water or milk can be given in rabies. The plant is claimed in the treatment of headache, mumps, pain, dropsy, madness, rigid thigh muscles, hemiplegia, epilepsy, convulsions, smallpox, syphilis, and hydrocele. Seeds used in hydrophobia, malaria. Roots are used to cure toothache and for brushing teeth [4, 5].
Scopolamine markedly increased spontaneous activity of rats and exhibited antiulcer activity against gastric ulcer. It inhibited gastric acid secretion and pepsin activity.

**Toxic effects**

*Datura metel* L. is a toxic herb that contains anticholinergic tropane alkaloids. Inappropriate consumption of this herb could result in anticholinergic intoxication. The clinical features of the datura plant poisoning are due to improper shodhana. Ingestion of *D. metel* in any form is dangerous and should be treated with caution. Impure datura shows the more anticholinergic symptoms like dryness of the mouth, laryngeal edema, hoarseness of voice, excessive thirst, cramps, dilatation of pupils, dryness of skin, unconsciousness and giddiness, narcosis and finally death. *Datura metel* may be toxic if ingested in a tiny quantity, symptomatically expressed as flushed skin, headaches, hallucinations, and possibly convulsions or even a coma.

**Antidote**

Cow’s milk with sugar, Vacha churna with curd, the paste of samudraphala triturated in cow’s urine is the antidote for datura poisoning.

**Parts used**

Leaves, seed, root are used in the treatment.

**Dosage**

Seed powder 25 mg - 50 mg. It is taken along with cow’s milk.
Important formulations

Lakshmivilas rasa, Mahajiwarankusha, Kanaksundar, Kanakäsava, Sutaekhara rasa, Mahavisagarbha taila, Unmattaras, Unmadgajankusha rasa etc.

Scientific reports on *datura metel var. fastuosa*

It is reported that three withanolide glycosides named daturametelins H-J (1-3), together with two known ones, daturataturin A (4) and 7, 27-dihydroxy-1-oxowitha-2, 5, 24-trienolide (5), were isolated from the MeOH extract of the aerial parts of *Datura metel* L. The compounds 1-5 were reported to possess antiproliferative activity against the human colorectal carcinoma (HCT-116) cell line. The non-glycosidic compound 5 exhibited the highest activity of the tested withanolides, with an IC (50) value of 3.2+/−0.2 microM [50, 51].

It is reported that a novel compound 2-(3, 4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate was isolated from the plant. The compound was found to be active against all the species tested, namely Candida albicans, Candida tropicalis, Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger. The MIC at which more than 90% of growth was inhibited [MIC (90)] by the compound ranged from 21.87 to 43.75 µg/ml against various fungal species by microbroth dilution assay. Since the compound 2-(3, 4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate has
antifungal activity. It may be explored further to develop new antimycotic drugs [52].

The leaves contain pyrrole derivative 1 which was characterised as 2 beta-(3, 4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1'-methylethyl pentanoate. The compound reported to antifungal activity and its MIC was found to be 87.5 µg/ml. Two proteins having mol. weights of 42 and 58 kD of Aspergillus fumigatus are potential targets for compound 1 [53].

Methanolic extracts of datura is reported to inhibit the growth of Aspergillus fumigatus, A. flavus and A. niger and their in vitro MICs were found to be 1.25-2.50 mg/ml by both microbroth dilution and % spore germination assays. By disc diffusion assay, a concentration of 0.062 mg/disc of methanol extract of D. metel plant showed significant activity against Aspergilli [54].

It is reported that the seed powder of the plant is having hypoglycemic activity in normal and alloxan-induced diabetic rats. The hypoglycemic effect was found to be dose dependent with all treatments at the doses administered [55].

It is reported that the plant contains Calystegine A (3), B (1), B (2) & B (3) [56].

The literature review revealed that, datura plant is highly useful in treatment of several ailments. But the toxicity associated with it limited its use. However Ayurvedic science adopted this plant since
the ages in the treatment of various diseases only after subjecting it to proper detoxification process. But there are no scientific data regarding detoxification of datura and its impact on the phytochemical and pharmacological profile. Therefore an attempt is made in the present study assess the influence of detoxification on the toxicity, therapeutic uses and chemistry of datura.

In the present study various biochemical parameters are used to assess the influence of detoxification of study drugs. Hence, relevant literature on such parameters is recorded in the following pages.

In the present study, several pharmacological parameters were assessed to analyse the influence of shodhana on all the three study plants. Various parameters assessed are:

1). Gastroprotective activity
2). Hepatoprotective activity
3). Nephroprotective activity
4). Cardioprotective activity
5). Anti-hyperlipidemic activity
6). Analgesic activity
7). Anti-inflammatory activity

Therefore relevant literature on above activities was summerised in the following pages.
2.2.4. LIVER

Diseases of Liver [59, 60]

The liver diseases are due to degeneration of the hepatocytes, vascular cells or bile ducts. The most important hepatic diseases are

1. Biliary obstruction
2. Metabolic disorder caused by genetic disease or exogenous substance, such as alcohol.
3. Inflammation, especially caused by Hepatitis viri
4. Liver cirrhosis
5. Liver neoplasia

Modern allopathic system of medicine has evolved phenomenally. However it is not in a position to give remedies for several diseases. Hepatic disorders are one such group of diseases which are treated worldwide by using alternative system of medicines. Several civilizations have been using herbs/herbal products to treat hepatic diseases since the ages. But no scientific basis has been established for the usage of many such herbs for the purpose. Therefore, many herbs/herbal products claimed to be useful in the treatment of liver disorders are being screened for their claimed hepato-protective potential. Several chemo-toxoins induced liver toxicity has been developed as experimental animal models to screen liver protective potential of various extensively employed herbs. The experimental
models of hepatotoxicity extensively use are explained in the following pages.

**Table no. 2.2.4.1**

**Clinical consequences of liver disease** [61]

<table>
<thead>
<tr>
<th>Characteristics signs</th>
<th>Hepatic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice and cholestasis</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td></td>
<td>Hyperammonemia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Fetor hepaticus</td>
</tr>
<tr>
<td>Palmar erythema</td>
<td>Spider angiomas</td>
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<tr>
<td></td>
<td>Hypogonadism</td>
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<tr>
<td></td>
<td>Gynecomastia</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Portal hepertension from cirrhosis</td>
<td>Ascites</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Hemorrhoids</td>
</tr>
<tr>
<td></td>
<td>Caput medusae-abdominal skin.</td>
</tr>
<tr>
<td>Life-threatening complications</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td></td>
<td>Multiple organ failure</td>
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<tr>
<td></td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Hepatorenal syndrome</td>
</tr>
</tbody>
</table>
### Table – 2.2.4.2

**Laboratory evaluation of liver disease** [62]

<table>
<thead>
<tr>
<th>Test category</th>
<th>Serum measurement</th>
</tr>
</thead>
</table>
| Hepatocyte integrity          | Cytosolic hepatocellular enzymes<br />
|                               | *Serum aspartate aminotransferase* (AST)*<br />
|                               | *Serum alanine aminotransferase* (ALT)*<br />
|                               | *Serum lactate dehydrogenase* (LDH)*<br />
| Biliary excretory function    | Substances normally secreted in the serum bilirubin<br />
|                               | Total : unconjugated plus conjugated*<br />
|                               | Direct : conjugated only*<br />
|                               | Urine bilirubin*<br />
|                               | Serum bile acids*<br />
|                               | Plasma membrane enzymes<br />
|                               | (from damage to bile canaliculus)<br />
|                               | *serum alkaline phosphatase*<br />
|                               | *serum γ-glutamyl transpeptidase*<br />
|                               | *serum 5-nucleotidase*<br />
| Hepatocyte function           | Proteins secreted in to the blood *serum albumin*<br />
|                               | *Prothrombin time* (factors V, VII, X, prothrombin, fibrinogen)<br />
|                               | Hepatocyte metabolism<br />
|                               | Serum ammonia*<br />
|                               | Aminopyrine breath test (hepatic demethylation)*<br />
|                               | Galactose elimination (intravenous injection)*<br />

The most common tests are in italics.<br />
*An elevation implicates liver disease.<br />
*A decrease implicates liver disease.
Table – 2.2.4.3

Hepatoprotective herbal formulations

<table>
<thead>
<tr>
<th>Herbal formulation along with their composition of herbs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jingrine</strong></td>
</tr>
<tr>
<td>Careya arborea</td>
</tr>
<tr>
<td>Cassia occidentalis</td>
</tr>
<tr>
<td>Cichorium intybus</td>
</tr>
<tr>
<td>Cusuta reflexa</td>
</tr>
<tr>
<td>Foeniculum vulgare</td>
</tr>
<tr>
<td>Phyllanthus amarus</td>
</tr>
<tr>
<td>Plantago major</td>
</tr>
<tr>
<td>Tamarix dioica</td>
</tr>
<tr>
<td>Solanum nigrum</td>
</tr>
<tr>
<td>Rubia cordifolia</td>
</tr>
<tr>
<td>Vitex negundo</td>
</tr>
<tr>
<td>Rosa damascena</td>
</tr>
<tr>
<td>Solanum xanthocarpum</td>
</tr>
<tr>
<td><strong>Liv-52</strong></td>
</tr>
<tr>
<td>Capparis spinosa</td>
</tr>
<tr>
<td>Cassia occidentalis</td>
</tr>
<tr>
<td>Cichorum intybus</td>
</tr>
<tr>
<td>Mandur bhasma</td>
</tr>
<tr>
<td>Solanum nigrum</td>
</tr>
<tr>
<td>Terminalia arjuna</td>
</tr>
<tr>
<td>Tamarix gallica</td>
</tr>
<tr>
<td><strong>Livex</strong></td>
</tr>
<tr>
<td>Aconitum heterophyllum</td>
</tr>
<tr>
<td>Andrographis paniculata</td>
</tr>
<tr>
<td>Cassia occidentalis</td>
</tr>
<tr>
<td>Cichorium intybus</td>
</tr>
<tr>
<td>Embelia ribes</td>
</tr>
<tr>
<td>Tephrosia purpurea</td>
</tr>
<tr>
<td>Piper longum</td>
</tr>
<tr>
<td>Solanum nigrum</td>
</tr>
<tr>
<td>Tamarix gallica</td>
</tr>
<tr>
<td><strong>Livp-7</strong></td>
</tr>
<tr>
<td>Andrographis paniculata</td>
</tr>
<tr>
<td>Aphanamixis rohituka</td>
</tr>
<tr>
<td>Azadirachta indica</td>
</tr>
<tr>
<td>Boerhaavi diffusa</td>
</tr>
<tr>
<td>Eclipta alba</td>
</tr>
<tr>
<td>Fumaria indica</td>
</tr>
<tr>
<td>Picrorhiza kurroa</td>
</tr>
</tbody>
</table>
Various experimental models used in the preclinical evaluation of hepatoprotective activity are

1). CCl₄ induced hepatitis in rats
2). Paracetamol
3). INH
4). Ethanol
5). D-galactosamine
6). Thiocetamide

In the present study CCl₄ induced hepatic damage in rats is used for assessing hepatoprotective activity. The mechanism of action of CCl₄ induced hepatic damage is discussed below.
Methods of pharmacological evaluation of hepatoprotective plants in-vivo models

Mechanism of carbon tetrachloride induced hepatotoxicity

CCl$_4$ is a potent hepatotoxin producing centrilobular hepatic necrosis, which causes liver injury [66].

CCl$_4$ induces fatty liver and cell necrosis and play a significant role in inducing triacylglycerol accumulation, depletion of GSH, increased lipid peroxidation, membrane damage and depression of protein synthesis and loss of enzyme activity. Being cytoplasmic in location the damage of cells release marker enzymes GOT, GPT and HDL in the serum [67].

It is now generally accepted that the hepatotoxicity of CCl$_4$ is the result of reductive dehalogenation, which is catalyzed by cytochrome P450 enzyme and form highly reactive trichloromethyl free radical. This then readily interacts with molecular oxygen to form the trichloromethyl peroxy radical. This free radical can form covalent bond with sulfahydryl group, such as glutathione (GSH), protein thiol and lipids or abstracting a hydrogen atom from an unsaturated lipid. This covalent binding of free radical to cell macromolecules is considered the initial step in a chain of events, which eventually leads to membrane lipid peroxidation, liver damage and finally cell necrosis [68-72].

CCl$_4$ is reductively converted by CYP P450 to the trichloromethyl radical. First the radical add covalently to
unsaturated fatty acids, trichloromethyl fatty acids, particularly of membrane phospholipids.

_**Fig no 2.2.4.1**_

**Schematic representation of reactive mechanism of CCl₄ induced hepatic injury** [66]

![Diagram of reactive mechanism of CCl₄ induced hepatic injury]

Recently these substituted fatty acids have been noted to be partially resistant to replace from endoplasmic reticular phospholipase A₂.

This seems to be result of cross linking of trichloromethyl fatty acid radical, which adds to double bond of other adjacent fatty acids.

The physiologic significance of this cross-linking on membrane structure and function may be of great importance, particularly if
these phospholipids are transformed to other critical sites in the cell. Besides covalent binding to lipid, the cells can abstract an electron from unsaturated fatty acids, yielding CHCl₃ and or fatty acid radical. Either the trichloromethyl fatty acid radical or the fatty acid radical can react with oxygen to form peroxy radical, which initiates the lipid peroxidation chain reaction [71].

To understand the whole process of hepatic damage, CCl₄-induced liver damage was modeled in monolayer cultures of rat primary hepatocytes with a focus on involvement of covalent binding of CCl₄ metabolites to cell components and/or peroxidative damage as the cause of injury.

1. Covalent binding of 14C-labelled metabolites was detected in hepatocytes immediately after exposure to CCl₄.
2. Low oxygen partial pressure increased the reductive metabolism of CCl₄ and thus covalent binding.
3. [14C]-CCl₄ was bound to lipids and to proteins throughout subcellular fractions. Binding occurred preferentially to triacylglycerols and phospholipids with phosphatidylcholine containing the highest amount of label.
4. The lipid peroxidation potency of CCl₄ revealed subtle differences compared to other peroxidative substances, viz., ADP-Fe³⁺ and cumol hydroperoxide respectively.
5. CCl₄, but not the other peroxidative substances, decreased the rate of triacylglycerol secretion as very low density lipoproteins.
The anti-oxidant vitamin E (α-tocopherol) blocked lipid peroxidation, but not covalent binding, and secretion of lipoproteins remained inhibited.

The results confirm that covalent binding of the CCl₃* radical to cell components initiates the inhibition of lipoprotein secretion and thus steatosis, whereas reaction with oxygen, to form CCl₃-OO*, initiates lipid peroxidation. The two processes are independent of each other, and the extent to which either process occurs depends on partial oxygen pressure. The former process may result in adduct formation and, ultimately, cancer initiation, whereas the latter results in loss of calcium homeostasis and, ultimately, apoptosis and cell death [71-74].

The parameters used for assessing the hepatic functioning used in the present study are

1). AST
2). ALT
3). ALP
4). Total & direct bilirubin
5). Cholesterol
6). Tissue GSH & LPO
7). Histopathological observations
Various animal models used for assessing nephroprotective property are

1). Cisplatin
2). Gentamycin
3). Paracetamol
4). INH
5). Rifampicin

In the present study cisplatin induced nephrotoxicity in rats is used for assessing nephroprotective activity. Therefore mechanism of cisplatin induced nephrotoxicity is discussed below.

Cisplatin induced renal injury

Cis diamino dichloro platinum 11 or cisplatin is a divalent inorganic water soluble platinum containing complex. It is an antineoplastic agent that has remarkably broad spectrum of clinical activity in the treatment solid tumors like testicular and ovarian carcinomas. Cisplatin is also been an important component in the treatment of bladder carcinoma, squamous cell carcinoma of head and neck, bronchogenic carcinoma, cervical and endometrial carcinomas and lymphomas. It is a cell cycle specific agent acting at the S-phase. The mechanism of antineoplastic activity is by forming platinum
complexes, which reacts with DNA forming intrastrand and interstrand cross link forming DNA adducts, which inhibits DNA replication and transcription to DNA breaks and miscoding [77].

Cisplatin enters the cell by the process of diffusion. Cisplatin causes myelosuppression, nausea, vomiting, peripheral neurophathy, ototoxicity and anaphylaxis. One of the major and limiting toxic effects of cisplatin is nephrotoxicity. Cisplatin is freely filterable at the glomerulus because of its low molecular weight and unchanged character. In addition cisplatin also gets excreted via tubular secretion. Hence the drug, gains access to renal tubular cell by means of secretion or reabsorption. The intracellular concentration of cisplatin is higher than the extracellular concentration in the rat kidney. The nephrotoxicity is produced because of the accumulation and retaining of platinum in the kidney, which is the predominant excretory route of cisplatin [77-80].

Histopathological coagulative necrosis, interstitial edema and tubular dilatation are the most prominent findings. The electron microscopic observation has shown swollen degenerated and vacuolated mitochondria in tubular cells as well as disruption of brush border of micro villi. Hence acute tubular necrosis is the main feature of cisplatin nephrotoxicity which is clinically manifested by elevation of blood urea nitrogen, serum creatinine, protein urea and hyperuricemia [74,75,76].
Mechanism of cisplatin induced nephrotoxicity

Cisplatin is a potent and valuable chemotherapy agent used to treat a broad spectrum of malignancies. Multiple mechanisms contribute to renal dysfunction following exposure to cisplatin. These include cellular toxicity, vasoconstriction in the renal microvasculature, and proinflammatory effects [85].

Lipid peroxidation (LPO) is generally assessed as increase in malondialdehyde (MDA) levels. The increase in MDA is always accompanied by cisplatin-induced tissue damage in both in-vivo and in-vitro studies. Although these studies suggest that LPO is a pathway in the onset of cisplatin-induced renal damage, its causal role in cisplatin nephrotoxicity is queried. In a study of isolated rat proximal tubules and inner medullary collecting duct cells, both cell types exhibited effects on mitochondrial respiration, upon cisplatin treatment. But cisplatin has elevated MDA only in proximal convoluted tubule and lytic plasma membrane damage as indicated by release of Cr. N,N'-Diphenyl-p-diphenylenediamine (DPPD). The alpha tocopherol have been reported to atleast partially ameliorate cisplatin toxicity. It has been reported that cisplatin causes increase in LPO and decrease in p-aminohippurate (PAH) uptake in rat renal cortical slices. It was also found that cisplatin did not increase enzymatic and nonenzymatic system-dependent LPO in-vitro and elevation of lipid peroxide levels was attributable to a decrease in the activity of lipid peroxide protecting enzymes such as superoxide dismustase,
glutathione peroxidase, glutathione transferase and catalase [78, 79]. Unlike most other forms of nephrotoxicity, glutathione (GSH) depletion is not a prominent feature of cisplatin nephrotoxicity. The majority of studies have described either normal or elevated GSH levels after cisplatin, suggesting that GSH turn over is retarded. Consistent with this, glutathione reductase, glutathione peroxidase and glutathione transferase were all inhibited after cisplatin treatment. Cisplatin inhibits activities of antioxidant enzymes in rat kidneys suggesting that cisplatin cytotoxicity results from generation of reactive oxygen species [84].

The parameters used for assessing nephroprotective are

1). Serum creatinine
2). BUN
3). Change in body weight & kidney weight
4). Tissue GSH & LPO
5). Histopathological observations
2.2.6. Stomach [75]

Gastrointestinal disorders are one of the severe classes of human ailments causing maximum discomfort, morbidity and mortality. Peptic ulcer is one such gut disorder. Peptic ulcer is a benign lesion of gastric or duodenal mucosa occurring at a site where the mucosal epithelium is exposed to acid and pepsin. There are several causes including, stress, alcohol consumption, cigarette smoking, H. pylori infection, ingestion of drugs and chemicals. Especially consumption of alcohol for a prolonged period, smoking of cigarettes, or chronic consumption of NSAIDs are causing peptic ulcers. The role of free radicals in the pathogenesis of peptic ulcer due to mucosal damage is established. The symptoms of peptic ulcer are: severe pain and irritation in the upper abdomen. If it is not treated properly, it may results in perforations in the wall of the gastrointestinal tract. Therefore, normally chronic dietary control and pharmacotherapeutic management is adopted for treating peptic ulcer. Now it is a trend to think of antioxidants in treating peptic ulcer. However no such agent is available for clinical practice. However, several side effects like arrhythmias, impotence, gynaecomastia, haematopoetic changes etc. associated with the various synthetic drugs used in the management of peptic ulcer is restricting the chronic usage of these agents.
A gastrointestinal lesion is not necessarily an ulcer. Lesions that don't extend below the mucosal lining (epithelium) are called erosions. Lesions of both acute and chronic ulcers can extend through the epithelium and perforate the stomach wall. Chronic ulcers also have scar tissue at the base.
**Peptic ulcer**

It is a chronic inflammatory condition involving a group of disorders characterised by ulceration in regions of upper gastrointestinal tract where parietal cells secrete pepsin and hydrochloric acid.

**Different factors related to acid secretion** [75,87]

a) **General factor:**
1. Vagal hormonal effect, histamine and epinephrine, insufficient circulation, shock and general ischemia increase the acid secretion.
2. Constitutional and environmental factors i.e. sex, age, temperature, family history, social class, geographical differences; occupation may also influence the acid release.
3. Local factors in stomach.
   a) **Aggressive factors:** HCl, pepsin, refluxed bile, pancreatic proteolytic enzymes, NSAID, alcohol, ingested irritants, bacterial toxins, physiochemical trauma; all of these factors increase the acid secretion.
   b) **Digestive factors:** Mucus, blood flow, resolution of epithelium, bicarbonates, the current status of drug therapy.
Drugs used in ulcer treatment

Various classes of drugs used in the treatment of ulcers are summarised in the following table.

<table>
<thead>
<tr>
<th>Established drugs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Anticholinergic</td>
<td>Pirenzine, telenzipine</td>
</tr>
<tr>
<td>2) H\textsubscript{2} receptor blocker</td>
<td>Cemitidine, rantidine, fomitidine</td>
</tr>
<tr>
<td>3) K\textsuperscript{+} / H\textsuperscript{+} ATPase blocking agents</td>
<td>Omeprazole, lansaprazole</td>
</tr>
<tr>
<td>4) Prostaglandins</td>
<td>Misoprostol, enprostil</td>
</tr>
<tr>
<td>5) Antacids</td>
<td>NaHCo\textsubscript{3}, Mg. hydroxide.</td>
</tr>
<tr>
<td>6) Coating agent</td>
<td>Sucralfate</td>
</tr>
<tr>
<td>7) Tricyclic antidepressant</td>
<td>Amitryptiline</td>
</tr>
<tr>
<td>8) Somatotatine analogue</td>
<td>Octreotide</td>
</tr>
</tbody>
</table>

Herbs with anti ulcer potential

1. Fruits extract of *Aegle marmelos* [88]
2. Roots extract of *Asparagus pubescens* [89]
3. Roots extract of *Guiera senegalensis* [90]
4. Leaves extract of *Mentha arvensis* [91]
5. *Tamrabhasma* an indigenous preparation of copper [92]
6. Roots extract of *Asparagus racemosus* [93]
7. Leaves extract of *Ocimum sanctum* [94]
8. Leaves extract of *Byrsonima crassa* [95]
9. Leaves extract of *Allophylus serratus* [96]
10. Whole plant extract of *Justicia prostrate* [97]
11. Leaves extract of *Piper betle* [98]
12. Roots extract of *Pongamia pinnata* [99]
13. Leaves extract of *Sapindus mukorossi* [100]
14. Fruits extract of *Benincasa hispida* [101]
15. Fruits extract of *Emblica officinalis* [102]
16. Antiulcer effect of *Shankha bhasma* [103]
17. Antiulcer activity of *Tephrosia purpurea* [104]
18. Antiulcer properties of *Ziziphus jujuba* Lam leaves [105]
19. Effect of standardized extract of *Ocimum sanctum* [106]
20. Antiulcer activity of *Digitrall* [107]
21. Aqueous decoction of *Mango flowers* as an antiulcer agent [108]
22. Antiulcer activity of *Indigofera aspalathoids* [109]
23. Antiulcer activity of certain *Phenyl tosylates* [110]
24. Antiulcer activity of two marketed *herbal products* [111]
25. Effect of *Rabeprazole* [112]
26. Antiulcer effect of *Amlodipine* [113]
27. Gastroprotective activity of *Spirulina platensis* [114]
28. Antiulcer activity of *Eranthemum roseum* [115]
In preclinical investigations several animal models of gastric ulcers have been used namely.

1). Ethanol induced ulcers in rats [116-120]
2). Pyloric ligation (Shay et al., rat model) induced ulcers [121-123]
3). NSAID induced ulcers in rats
4). Stress induced ulcers in rats

In the present study alcohol induced ulcers in rats and pyloric ligation induced ulcers in rats were adopted. Therefore relevant information on the mechanism of the ulceration in their two models is discussed here.

**Mechanism of ethanol induced gastric ulcer:**

The damage produced by ethanol to gastric mucosa is due to number of contributing factors, which includes effects on mucosal blood flow, platelet thrombi, damage to capillary endothelium, formation of mast cell secretory products [117], release of arachidonic metabolites specifically LCT₄/D₄, PAF [118] and generation of reactive oxygen species (ROS) [119].

Ethanol induced gastric lesion formation may be due to static in gastric blood flow which contributes to the development of the hemorrhage and necrotic aspect of tissue injury. Also, there is perturbation of superfacial mucosal cells, notably the mucosal mast cell leading to the release of vasoactive mediators including histamine, thus causing damage to gastric mucosa [120].
As ethanol induced ulcers are independent of luminal acid [139], the increase in mucosal protective factors should then be the major factors responsible for ulcer protection in this model.

**Fig. no 2.2.6.2**

*Figure showing ethanol induced gastric ulcer* [112]

**Mechanism of pylorus ligation induced gastric ulcer**

The causes of gastric ulcer after pyloric ligation are believed to be due to increase in gastric hydrochloric acid and pepsin secretion and / or stasis of acid [121]. According to Shay et al, the volume of secretion is also an important factor in the formation of ulcer due to exposure of the unprotected lumen of the stomach to the accumulating acid [122]. Involvement of the free radicals is also reported for gastric ulcers caused by pylorus ligation. The free radicals produced cause lipid peroxidation, leading to membrane fluidity which in turn increases the influx of Ca$^{2+}$ ions and result is the reduced membrane integrity of surface epithelial cells, thereby generating gastric ulcers [124].
**Fig. 2.2.6.3**

**Pylorus ligation induced ulcer** [122]

The parameters used for assessment of gastroprotective property of study drugs;

1. In pyloric ligation induced ulcers model
   i. Total volume of gastric secretions
   ii. PH of gastric secretion
   iii. Total and free acidity
   iv. Ulcer index of stomach tissue
   v. Tissue GSH & LPO

1. In ethanol induced ulcer model
   i. Ulcer index
   ii. Tissue GSH & LPO
2.2.7. HEART

Heart diseases

Heart disease or cardiopathy is an umbrella term for a variety of different diseases affecting the heart.

Cardiovascular disease [125,126]

Cardiovascular disease is any one of number of specific diseases that affect the heart itself and/or the blood vessel system, especially the veins and arteries leading to and from the heart. Research on disease dimorphism suggests that women who suffer with cardiovascular disease usually suffer from forms that affect the blood vessels while men usually suffer from forms that affect the heart muscle itself. Known or associated causes of cardiovascular disease include diabetes mellitus, hypertension, hyperhomocysteinemia and hypercholesterolemia.

Types of cardiovascular disease include:

Atherosclerosis

Thickening of the walls of arteries and loss of elasticity are the main characteristics of a group of diseases called atherosclerosis. One form of atherosclerosis a process in which smooth muscle cells proliferate and fatty substances, especially cholesterol and triglycerides (neutral fats), accumulate in the walls of medium-size and large size arteries. Atherosclerosis damage the endothelial lining of artery then smooth muscle proliferate and lipids build up and
accumulation of cholesterol and triglycerides cause atherosclerotic plaque. As it grows, a plaque obstructs blood flow in the affected artery. An additional damager is that the plaque provides a roughened surface that cause blood platelets to release platelet derived growth factor (PDGF) and aggravate atherosclerosis.

**Ischaemic heart disease**

- Ischaemic heart disease – another disease of the heart itself, characterized by reduced blood supply to the organs.

**Heart failure**

Heart failure, also called congestive heart failure (or CHF), and **congestive cardiac failure (CCF)**, is a condition that can result from any structural or functional cardiac disorder that impairs the ability of the heart to fill with or pump a sufficient amount of blood throughout the body, leading to the heart and body's failure.

**Hypertensive heart disease**

Main article: Hypertensive heart disease

Hypertensive heart disease is heart disease caused by high blood pressure, especially localised high blood pressure. Conditions that can be caused by hypertensive heart disease include:

- Left ventricular hypertrophy
- Coronary heart disease
- (Congestive) heart failure
- Hypertensive cardiomyopathy
• Cardiac arrhythmias

**Inflammatory heart disease**

Inflammatory heart disease involves inflammation of the heart muscle and/or the tissue surrounding it.

• Endocarditis: inflammation of the inner layer of the heart, the endocardium. The most common structures involved are the heart valves.

• Inflammatory cardiomegaly

• Myocarditis: inflammation of the myocardium, the muscular part of the heart.

**Valvular heart disease**

Valvular heart disease is disease process that affects one or more valves of the heart. There are four major heart valve which may be affected by valvular heart disease, including the tricuspid and aortic valves in the right side of the heart, as well as the mitral and aortic valves in the left side of the heart.

**Various models used for assessing cardioprotective activity**

1. Isoproterenol, Doxorubicin induced cardiac ischemia

2. Doxorubicin induced cardiac ischemia

3. Triton induced hypercholesterolemia

4. Dietary-induced hypercholesterolemia
5. Perfused guinea-pig Langendorff hearts subjected to ischemia and reperfusion.

6. Atherogenic diet induced hypercholesterolemia

In the present study isoproterenol induced cardiac ischemia is used, hence, the mechanism of it is described below.

Ischemic Heart Disease (IHD) is the leading cause of morbidity and mortality in worldwide and according to the world health organization it will be the major cause of death in the world by the year 2020 [125]. Myocardial Infarction (MI) results from the prolonged myocardial ischemia with necrosis of myocytes due to interruption of blood supply to an area of heart. Isoproterenol (ISO) induced myocardial necrosis is a well known standard model to study the beneficial effect of many drugs on cardiac dysfunction. ISO is a β-adrenergic agonist that causes severe stress in myocardium and necrotic lesions in the heart muscles. ISO induced myocardial injury involves membrane permeability alterations, which brings about the loss of functions and integrity of myocardial membranes. MI induced by ISO in rats has been shown to be accompanied by hyperglycemia, hyperlipidemia and increase in serum creatine phosphokinase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase activities. The mechanism proposed to explain isoproterenol induced cardiac damage involves generation of highly cytotoxic free radicals through auto-oxidation of catecholamine and has been implicated as one of the causative factor.
Various parameters used for screening cardioprotective property are

1. Tissue GSH & LPO

2. AST, ALT, Lactate dehydrogenase (LDH) & Creatine phosphokinase (CPK)

**Fig. 2.2.7.1**

**Figure showing heart disease and cardio protection**

Ischemia/reperfusion injury is influenced by major risk factors

<table>
<thead>
<tr>
<th>Ischemia/reperfusion</th>
<th>Ischemia/reperfusion injury:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• contractile dysfunction</td>
</tr>
<tr>
<td></td>
<td>• arrhythmias</td>
</tr>
<tr>
<td></td>
<td>• myocardial infarction</td>
</tr>
</tbody>
</table>

Cardioprotection by preconditioning

- < 120 min: “classic”
- 24-72 hours: “late”

<table>
<thead>
<tr>
<th>Cardioprotection by preconditioning</th>
<th>Cardioprotection:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• contractile function</td>
</tr>
<tr>
<td></td>
<td>• arrhythmias</td>
</tr>
<tr>
<td></td>
<td>• infarct size</td>
</tr>
</tbody>
</table>

Cardioprotection by postconditioning

Major risk factors such as hyperlipidemia, diabetes, heart failure, aging, etc interfere with cardioprotection conferred by pre- and postconditioning
Fig. 2.2.7.2

Figure showing myocardial infarction [124]
**Herbs with cardioprotective potential**

1. Fruits extract of *Piper longum* [127]
2. Fruits extract of *Cucumis trigonus* [128]
3. Whole plant extract of *Commiphora mukul* [129]
4. Leaves and nut extract of *Betel quid* [130]
5. Fruits extract of *Punica granatum* [131]
6. Leaves extract of *M.indica* (mangiferin) [132]
7. Fruits extract of *Embelia ribes* [133]
8. Leaves extract of *Muntingia calabura* [134]
9. Leaves extract of *Trichopus zeylanicus* [135]
10. Leaves extract of *Ocimum sanctum* [136]

The seeds of nux-vomica was claimed to possess organprotective properties [4, 5] therefore the plant was selected for assessing the influence of shodhana on organprotective and tissue antioxidant potential. The CCl₄ induced hepatotoxicity, cisplatin induced nephrotoxicity and pylorus ligation, ethanol induced gastric ulcer in rats were selected to assess the organ protective potential. The plant also claimed in pain and inflammation management in the treatment of rheumatoid arthritis [10,11]. Therefore the plant was selected for assessing the influence of shodhana on analgesic activity in acetic acid induced writhing effects and anti-inflammatory activity in carrageenan induced rat paw edema was screened.

The guggul posesses anticholesterol, cardioprotective, antiulcer and anti-inflammatory activities [4,5]. Therefore the guggul was selected for assessing anticholesterol activity in Triton WR-1339