CHAPTER 2

REVIEW OF LITERATURE
Cassia fistula
2.1 Medicinal Plants

2.1.1 Cassia fistula

Scientific name: *Cassia fistula*

Common Name: Indian Laburnum, Golden Shower, Garmao, Amultus

**Introduction**

*Cassia fistula* (Fabaceae, Caesalpinioideae), a very common plant is a semi-wild in nature and known for its medicinal properties. It is distributed in various regions including Asia, South Africa, China, West Indies and Brazil. It is deciduous and mixed-monsoon forests throughout greater parts of India, ascending to 1300 m in outer Himalaya, is widely used in traditional medicinal system of India. It is a deciduous tree with greenish grey bark, compound leaves; leaflets are each 5-12 cm long pairs. A semi-wild tree known for its beautiful bunches of yellow flowers and also used in traditional medicine for several indications. A fruit is cylindrical pod and seeds many in black, sweet pulp separated by transverse partitions. The long pods which are green, when unripe, turn black on ripening after flowers shed.

**Chemical Constituents**

Morimoto et al. isolated (-)-epiafzelechin, 3-O-B-D-glucopyranoside, 7 biflavonoids and two triflavonoids together with (-)-epiafzelechin, (-)-epicatechin and procyanidin B-2 from the leaves. The anthraquinones like Rhein, Chrysophanol and Physcion also found in the leaves of the plant. The leaves also contain free rhein, rhein glucoside and sennosides A and B. While rhein and its glucoside could be isolated in pure state, others are obtained as mixtures.

Glycerides with linoleic, oleic, palmitic and stearic acids as major fatty acids together with traces of caprylic and myristic acids has been found in the seeds.
The major carbohydrate known as galactomannan consisting of 8 different types of sugar moieties was reported in the seeds 7. It has been reported that the seeds of the plant contain the crude proteins like globulin and albumin 8. Rhein, a major anthraquinone derivative is isolated from the fruit pulp of the plant 9.

A bianthraquinone glycoside, fistulin together with kaempferol and rhein have been isolated from ethanol extracts of *Cassia fistula* flowers. Kaempferol and a proanthocyanidin have been also isolated from the acetone extract of the flower 10. It has been reported that the flowers of the plant contains a certain amount of alkaloids 11.

The stem bark of *C. fistula* is found to be a potential source of lupeol, β-sitosterol and hexacosanol 12. Fistucacidin, an optically inactive leucoanthocyanidin, which is a phenolic compound, was isolated from the heart wood of the plant 13. An isoprenoid compounds including 5-nonatetracontanone, 2-hentriacontanone, triacontane, 16-hentriacontanol and β- sitosterol along with oil possess antibacterial activity have also been isolated in *C. fistula* pods 14. A new diterpene, 3B-hydroxy-17-norpimar-8(9)-en-15-one was isolated from the pods of the plant 15. The structure of a new colouring matter, fistulic acid, an anthraquinone acid was elucidated from the pods 16.

**Structure of compounds present in Cassia fistula**

![Rhein](image)

![Epicatechin](image)

![Chrysophanol](image)

![Kaempferol](image)
Biological and Pharmacological properties

The leaf of the plant showed antibacterial action against *Escherrichia coli, Bacillus subtilis, Klebsiella aerogenes, Pseudomonas aerogenes and Proteus vulgaris*. Chloroform, ethyl acetate, hexane, methanol and water extracts of *Cassia fistula* flowers showed significant zone of inhibition against Gram-positive bacteria, *Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis, Enterococcus faecalis* and one Gram-negative bacterium *Pseudomonas aeruginosa*.

The antioxidant activity of 90% ethanol extracts of leaves and 90% methanol extracts of stem bark, pulp and flowers from *Cassia fistula* L were carried out. The antioxidant activity power was in the decreasing order of stem bark, leaves, flowers and pulp and it
was well correlated with the total polyphenolic content of the extracts. Aqueous extract of flowers of *C. fistula* was screened for its antioxidant effect in alloxan induced diabetic rats. The result of this study indicated promising antioxidative activity in alloxan diabetic rats.

The n-heptane extract of *Cassia fistula* leaves exhibited hepatoprotective activity in rats. The extract of *C. fistula* at a dose of 400 mg/kg exhibited significant hepatoprotective activity and it was comparable to that of a standard hepatoprotective agent. The Anthelmintic activity of methanol extract of *C. fistula* fruit pulp and seeds were investigated against *Pheretima postnuma* earthworm and it showed significant effect in dose dependent manner.

The methanolic extract of *C. fistula* pods showed antipyretic activity and it may be due to individual or combined action of bioactive constituent present in it. The antipyretic potential the chloroform, ethyl acetate, methanol and petroleum ether extracts of the bark was evaluated. It was observed that methanol extract at a dose of 300mg/kg body weight exhibited maximum antipyretic activity amongst other extracts which is statistically significant.

Anti-inflammatory and antioxidant activities of the aqueous and methanolic extract of bark of the *Cassia fistula* were assayed in Wistar albino rats. It was found that extracts possess significant anti-inflammatory effect in both acute and chronic models. Antifertility effect of ethanolic extract of leaf of *Cassia fistula* on the fertile male albino rats was investigated. The sperm count, the sperm vitality and the sperm motility were decreased after the treatment of *Cassia fistula* extract. Thus the *C. fistula* may be used as a male antifertility agent.

The petroleum ether extract of seeds of *Cassia fistula* was screened for the antifertility activity in proven fertile female albino rats and this study indicated that the petroleum ether extract of *Cassia fistula* seeds possesses pregnancy terminating effect by virtue of anti-implantation activity.
Wound healing potential of *Cassia fistula* on infected albino rat model was evaluated. The extract showed better wound closure and improved tissue regeneration at the wound site \(^{28}\).

**Medicinal and other uses**

Number of applications of various part of *cassia fistula* are found for medicinal and other purposes. The roots of *cassia fistula* have great curative effects against common cold. The pod is powdered and mixed with honey and consumed. This is very effective in curing cough \(^{29}\). Leaves are useful in jaundice, piles, and rheumatism ulcers and also externally used for skin diseases like skin eruptions, ring worms, eczema etc \(^{30}\).

The ripe pods and seeds are used as a laxative. The barks, roots, leaves and flowers also have laxative properties, but to a lesser extent \(^{31}\). The seeds are an emetic. The barks are used in tanning. The fruit is cathartic and applied in rheumatism and snake bite \(^{32}\).
Cinnamomum Zeylanicum
2.1.2 Cinnamomum zeylanicum

Scientific name: *Cinnamomum zeylanicum*

Common Name: Cinnamon, Ceylon cinnamon, Dalchini, True Cinnamon, Tvak

Introduction

*Cinnamon* (*C. zeylanicum*) is a small evergreen tree, 10-15 meters (32.8-49.2 feet) tall. It belongs to the family *Lauraceae*. *C. zeylanicum* originates from Ceylon (Sri Lanka), being also native to South-East India. Sri Lanka is the main provider of cinnamon, mainly exported as "cinnamon quills". It is an important spice and aromatic tree.

*C. zeylanicum* (Ceylon cinnamon) is sometimes called "true cinnamon". It has a much different flavor: a less sweet, more complex, citrusy flavor. Ceylon cinnamon is also known as “old-fashioned cinnamon”. Leaves are oblong – elliptic, ovate shapes dark glossy green. Cinnamon is the dried inner bark of an evergreen tree that is harvested during the rainy season when the bark is most flexible and easiest to work with. The fruit is a purple 1 cm berry containing a single seed. Leaf and bark are used as spices and for the production of volatile oils.

Chemical Constituents

Various chemical compounds are present in the different part of *C. zeylanicum*. The principal constituents of leaf bark and root oils are eugenol, cinnamaldehyde and camphor, respectively.

The steam-distilled volatile oil from cinnamon fruit stalks was analyzed with GC and GC-MS and it indicated the presence of hydrocarbons (44.7%) and oxygenated compounds (52.6%). (E)-Cinnamyl acetate (36.59%) and (E)-caryophyllene (22.36%) are found to be major compounds.
By using GC and GC-MS, the hydro-distilled volatile oil of the *C. zeylanicum* buds was analyzed and found that it consists of terpene hydrocarbons (78%) and oxygenated terpenoids (9%). α-Bergamotene (27.38%) and α-copaene (23.05%) are found to be the major compounds.

The steam-distilled oil of flowers of *C. zeylanicum* was analyzed by GC and GC-MS. It consists of 23% hydrocarbons and 74% oxygenated compounds. A total of 26 compounds constituting ≈97% of the oil were characterized. *(E)*-Cinnamyl acetate (41.98%), trans-α-bergamotene (7.97%), and caryophyllene oxide (7.2%) are found to be major compounds.

**Structure of compounds present in *Cinnamomum zeylanicum***

![Eugenol](image1)

![Cinnamaldehyde](image2)

![Camphor](image3)

![Cinnamyl acetate](image4)

![α-Copaene](image5)

![Caryophyllene](image6)
Biological and Pharmacological properties

Effect of essential oil of *C. zeylanicum* on some pathogenic bacteria was evaluated and found that the gram-positive bacteria were more sensitive than gram-negative bacteria to the essential oil of *C. zeylanicum* 44. Ethanol extract of cinnamon were found sensitive to *Pseudomonas sp.*, *E. coli*, *Bacillus subtilis* and *Staphylococcus aureus*. Acetone extract of cinnamon produced zone of inhibition against *Pseudomonas sp.*, *E. coli*, and *Bacillus subtilis* 45. Antibacterial activity of benzene, ethyl acetate, methanol and water extracts of *C. zeylanicum* were evaluated using pour plate method at 250, 500 and 1000 ppm concentrations against *Bacillus cereus*, *B. coagulans*, *B. subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. A broad spectrum of antibacterial activity has been exhibited by all these extracts. Ethyl acetate and benzene extract showed higher antibacterial activity than methanol and water extracts 46.

The essential oil of leaves *C. zeylanicum* exhibited high antifungal activity against *Aspergillus flavus* strains, inhibiting growth and conidia germination process, in addition to cause morphological changes in its cellular structure 47. Bark extract of *C. zeylanicum* showed the highest fungicidal activity with minimum inhibitory concentrations (MIC) value at 1.2 µg/mL against *C. gloeosporioides* and *B. theobromae* at 24, 48, and 120 hr after infection 48. *C. zeylanicum* also inhibited *C. albicans* most effectively 49.

Antioxidant and antimutagenic activities of fruit extracts (acetone, ethyl acetate, methanol and water) of *C. zeylanicum* was evaluated. Highest antioxidant was found in case of water extract and followed by methanol, acetone and ethyl acetate extracts. All the extracts decreased sodium azide mutagenicity in *Salmonella typhimurium* strain (TA100). At 5000 mg/plate all the extracts showed strong antimutagenicity 50.

*C. zeylanicum* has beneficial effects as a potential therapeutic agent for diabetes mellitus both *in vitro* and *in vivo*. It promotes better glycaemic control and healthy lipid parameters, reduces insulin resistance, potentiates the action of insulin and ameliorates common complications associated with diabetes 51.
It is reported that Type-A procyanidine polyphenols (TAPP) has immunomodulatory and anti-inflammatory potential \textit{in vitro}. TAPP isolated from the bark of \textit{C. zeylanicum} exhibited anti-inflammatory and anti-arthritic effects in animal models without ulcerogenicity potential \textsuperscript{52}.

Study was done to determine the effect of \textit{C. zeylanicum} on experimentally induced excision wounds in rats and found that the aqueous extracts was effective in treating experimentally induced wounds and hasten healing, showing a dose-dependent treatment trend \textsuperscript{53}.

**Medicinal and other uses**

The bark and the leaves of \textit{Cinnamomum} spp. are commonly used as spices in home kitchens and their distilled essential oils or synthetic analogs are used as flavoring agent in the food and beverage industry \textsuperscript{54}.

It is useful for treatment of diarrhoea and other problems of the digestive system. Cinnamon has traditionally been used to treat toothache and fight bad breath and also used for colds \textsuperscript{33}.

The bark of \textit{C. zeylanicum} has anti-inflammatory and astringent properties which effectively treat toothache and rheumatoid joint pains \textsuperscript{55}. Recent studies suggest that consuming as little as one-half teaspoon of Cinnamon each day may reduce blood sugar and cholesterol level \textsuperscript{56}.
Glycyrrhiza glabra
2.1.3 Glycyrrhiza glabra

**Scientific name:** Glycyrrhiza glabra

**Common name:** Atimadhura, Liquorice, Jethi-madha, Mulethi, Yashti Madhuka

**Introduction**

Glycyrrhiza glabra Linn. (Family: Papilionaceae/ Fabaceae) is a traditional medicinal herb grows in the various parts of the world. It is a hardy herb or under shrub, erect grows to about 2m height. The roots are long, cylindrical, thick and multibranched. The leaflets are arranged in pairs along a central axis. Flowers are light blue to violet. Fruits are reddish-brown.

Glycyrrhiza glabra is native to Eurasia, Northern Africa and Western Asia. It is also cultivated as a crop plant, particularly in Russia, Spain and the Middle East. Its scientific name is taken from the Greek for sweet root (glykys, meaning sweet, and rhiza, meaning root). It has been used medicinally in both Western and Eastern countries for more than 4000 years.

**Chemical Constituents**

Different types of constituents have been isolated from G. glabra, including a water-soluble, biologically active complex that accounts for 40-50% of total dry material weight. This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances.

Root contains triterpenoid saponins (4–20%), mostly glycyrrhizin, a mixture of potassium and calcium salts of glycyrrhizic acid (also known as glycyrrhizic or glycyrrhizinic acid, and a glycoside of glycyrrhetinic acid) which is 50 times as sweet as sugar.

The flavonoid content of the plant is the responsible for the yellow colour of licorice which includes liquiritin, isoliquiritin (a chalcone) and other compounds like neoisoliquiritin, licuraside, glabrolide and licoflavonol.
Isoflavonoid derivatives are also present in licorice which includes glabridin, glabrene, glabrone, shnipterocarpin, licoisoflavones A and B, formononetin, glyzarin, and kumatakenin \(^{64}\).

*G. glabra* contains various coumarin compounds which include glabrocoumarone A and B, glycyrin, liqcoumarin, herniarin, umbelliferone \(^{65}\), glycocoumarin, licofuranocoumarin, licopyranocoumarin \(^{66, 67}\) and glabrocoumarin \(^{68}\). *G. glabra* extract contains fatty acids (C\(_2\)-C\(_{16}\)) and phenols (phenol, guaiacol), together with common saturated linear \(\gamma\)-lactones (C\(_6\)-C\(_{14}\)) and also contain new series of 4-methyl-\(\gamma\)-lactones and 4-ethyl-\(\gamma\)-lactones in trace amounts has also been found \(^{69}\).

**Structure of compounds present in *Glycyrrhiza glabra***

![Glycyrrhizin or glycyrrhizic acid](image)

![Glycyrrhetinic acid](image)

![Glabridin](image)

![Glabrene](image)

![Licoflavonol](image)

![Glabrone](image)
Biological and Pharmacological properties

The methanol extract of aerial parts of *G. glabra* exhibited antibacterial activity against various types of bacteria. Glabridin, glabrene and licochalcone A exhibited antimicrobial activity against *Helicobacter pylori* in vitro. The alcohol extract of the roots of *G. glabra* was found to possess antifungal activity against *Candida albicans* and against other fungi *Arthrinium sacchari* and *Chaetonmium funicola*. Glabridin showed resistance modifying activity against drug resistant mutants of *Candida albicans* at a minimum inhibitory concentration of 31.25–250 μg/mL.

Seven constituents, with antioxidant capacity were isolated from *Glycyrrhiza glabra*. The isolated compounds were identified as the isoflavans Hispaglabridin A, Hispaglabridin B, Glabridin and 4’-O-Methylglabridin, the two chalcones, isoprenylchalcone derivative and Isoliquiritigenin and the isoflavone, Formononetin. Among these compounds, Glabridin was found as the most abundant and potent antioxidant. Glycyrrhizin and
glibridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation.\textsuperscript{75, 76}

Glycyrrhizic acid, a component obtained from \textit{G. glabra} showed antiviral activity. It inhibits growth and cytopathology of several unrelated DNA and RNA viruses, while not affecting cell activity and ability to replicate. Glycyrrhizic acid also inactivates herpes simplex virus particles irreversibly.\textsuperscript{77}

Ethanol extract obtained from the \textit{roots of G. glabra} exhibited the anticonvulsant effect.\textsuperscript{78} Glycyrrhizic acid possesses anticonvulsant property against PTZ(Pentylene tetrazole) & INH induced convulsions.\textsuperscript{79}

Hepatoprotective effect of aqueous extract of \textit{G. glabra} roots in rabbit models with acute liver injury induced by Carbon tetrachloride has been reported. The aqueous extract of \textit{G. glabra} had a significant effect in amioleating liver functions as well as restoring hepatic tissue in acute liver diseases. Thus, it can be used for prevention and treatment of liver disorders.\textsuperscript{80}

Liquorice extract has been used for peptic ulcer and as an alternative to bismuth that has a protective role against acid and pepsin secretions by covering the site of lesion and promoting the mucous secretion.\textsuperscript{81}

\textit{G. glabra} accelerated the metabolism of cells in the bone marrow erythroid stem and increased the animal’s resistance to stress.\textsuperscript{82} Licorice exhibited an antiplatelet aggregation effect.\textsuperscript{83, 84}

**Medicinal and other Uses**

The Greek botanist Theophrastus, who lived in the fourth century BC, stated that licorice could be used to quench thirst and treat asthma, dry cough, and other respiratory diseases. He also said it could be used to heal wounds when mixed with honey.\textsuperscript{85} Liquorice is the most commonly useful for treatment of upper respiratory ailments including coughs, hoarseness, sore throat and bronchitis.\textsuperscript{86, 87}
Licorice (*G. glabra*) and its extract are used in gastrointestinal diseases and also as liver and bile remedies and urological remedies in the Western countries.

It also helps to maintain a balance in the estrogen levels in the body, as high levels of this hormone can cause menstrual problems. It is widely used for treatment of peptic ulcer. Due to strong anti-inflammatory actions; liquorices root is an indispensable herbal remedy against autoimmune diseases. It is useful in treatment of early Addison disease (chronic adrenal insufficiency). It has been used in herbal medicine for skin eruptions, including dermatitis, eczema, pruritus and cysts.

Liquorice is also used as filler in capsules and added to medicines as a sweetener to mask the unpleasant taste of other ingredients.
Nerium Indicum
2.1.4 Nerium Indicum

**Scientific Name:** *Nerium indicum*

**Common Name:** Indian Oleander, Kaner, Karavi, Harapriya, Kanher

**Introduction:**

*Nerium indicum* belongs to Apocynaceae family and it is a large evergreen shrub with milky juice. It is popularly known as Karavira in Sanskrit, Indian oleander in English and kaner in Hindi. The leaves are long, linear-lanceolate, 10-15 cm in length with horizontal nerves. Flowers are white, pink or red in colour, sweet smelled and 4-5 cm in diameter. Fruits are long about 15-20 cm, cylindrical and paired growing with the stem. Seeds contained in fruit are numerous, compressed and white in colour having smooth hairs.

This plant has many therapeutic applications. Leaves have been applied externally in the treatment of scabies and to reduce swellings. The leaves and the flowers are cardiotonic, diaphoretic, diuretic, emetic, expectorant and sternutatory.

**Chemical constituents**

The leaves contain neriin and oleandrin; both are cardiac glycosides with properties similar to digitalin. Leaves also contain ursolic acid that is similar to rutin.

Bark contain two toxic principles neriodorin and neriodorein. Another toxic principle is karabin. Both karabin and neriodorin are probably resins. The alcoholic extract of bark showed presence of \( \alpha \)-amyrin, \( \beta \)-Sitosterol in petroleum ether fraction, Kaempferol in the ether fraction and odoroside in the chloroform fraction.

The seeds contain phytosterin and l-strophnathin. The roots contain bitter glycosides fenolinic acid and aromatic oil.
Structure of compounds present in *N. indicum*

![Oleandrin](image1.png) ![α-amyrin](image2.png)

- Oleandrin
- α-amyrin

![β-Sitosterol](image3.png) ![Kaempferol](image4.png)

- β-Sitosterol
- Kaempferol

**Biological and Pharmacological properties**

The alcoholic extract of leaves of *Nerium indicum* was effectively inhibited the growth rate of *Staphylococcus aureus*, *Candida albicans*, *Aspergillus niger*, *Mucor*, *Rhizopus* and *Penicillium species* even at lower concentrations. It was found that ethanol extract of *N. indicum* leaves showed higher zone of inhibition than benzene extract against *Bacillus subtilis*.

The methanol extract of flowers of *Nerium indicum* showed inhibition of *Bacillus sp.*, *Escherichia coli*, *Yersinia sp.*, *Staphylococcus sp.* at 500ppm and 1000ppm, whereas no
inhibitory effect was observed against \textit{Pseudomonas sp.}, \textit{Lactobacillus sp.}, \textit{Enterococcus sp.}, and \textit{Klebsiella sp} \textsuperscript{102}.

The study on antioxidant activity of methanolic extract of \textit{Nerium indicum} leaves was carried out by using DPPH free radical scavenging, superoxide anion scavenging and reducing power assay. It was found that \textit{Nerium indicum} showed very significant radical scavenging activity compared to the control \textsuperscript{103}. Methanolic extract of flowers of \textit{N. indicum} was analysed for antioxidant activity and the results clearly indicated that the methanol extracts of Nerium indicum flowers have more potent antioxidant activity than leaves \textsuperscript{103}.

The flowers extract of \textit{Nerium indicum} was analyzed for antiulcer activity in rats in which gastric ulcers were induce by oral administration of indomethacin and pylorus ligation. Flowers extract of \textit{Nerium indicum} was administered in the dose of 500 and 1000 mg kg\textsuperscript{-1} orally 30 min prior to ulcer induction. The antiulcer activity was assessed by determining and comparing the ulcer index in the test group with that of the vehicle control group. Gastric total acidity and free acidity were estimated in pylorus ligated rats. Cimetidine was used as a reference drug and it was found that methanolic flowers extract of \textit{Nerium indicum} possesses significant antiulcer activity \textsuperscript{104}.

The study on analgesic activity of methanolic extract of \textit{N.indicum} leaves showed significant peripheral analgesic activity. The mechanism of analgesic activity action of \textit{Nerium indicum} may be due to its inhibitory effect on the synthesis of prostaglandins and leukotrienes \textsuperscript{105}.

Rajbhandari, M., et al carried out screening of 23 Nepalese medicinal plants for antiviral activity and it was found that methanolic extract of leaves of \textit{N. indicum} exhibited considerable antiviral activity against herpes simplex virus and influenza virus \textsuperscript{106}.

Sikarwar, M. S., et al. studied the antidiabetic activity of chloroform and ethanol extract of \textit{Nerium indicum} leaf in alloxan induced diabetic albino rats. A comparison was made.
between the action of *Nerium indicum* extracts and a known antidiabetic drug glibenclamide. Both extracts showed significant antidiabetic activity\(^{107}\).

Methanolic flowers extract of *Nerium indicum* was evaluated for hepatoprotective in rats. The plant extract showed a remarkable hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in liver tissues\(^{108}\).

Pooja, S., et al. tested extracts of flowers of *N. indicum* orally in albino mice at the dose level of 400 mg/kg body weight for Central nervous system activity. Significant anticonvulsant activity was seen as there was a delay in the onset of Pentylene tetrazole and Maximal electroshock induced seizures as well as decrease in the severity. Significant decrease in the locomotor activity was also observed on oral administration of plant extract. No mortality was seen up to the dose level of 2000 mg/Kg. These results reveal the anticonvulsant and sedative activity of the extract\(^ {109}\).

**Medicinal and other Uses**

There are various medicinal uses of *Nerium indicum*. A decoction of the leaves is useful externally in the treatment of scabies and to reduce swellings. Leaves and flowers are also used to treat malaria and as traditional medicine it induces the termination of embryo. Leaves and flowers are thought to have actions as tonic, cardio tonic, diaphoretic, diuretic, emetic and expectorant. Leaves are powerful repellent.

The root powder is an external remedy for hemorrhoids and ulcers around genitals. Leaves and bark is treated as insecticide, rat poison and parasitic. A green dye is obtained from the flowers. It is used in skin related problems and also helps in healing of wounds and also helps in reducing inflammation\(^ {110,111}\).
Terminalia Chebula
2.1.5 Terminalia chebula

**Scientific name:** *Terminalia chebula* Retz.

**Common name:** Abhaya, Pathya, Haritaki, Harad, Harade, Myrobalan

**Introduction**

*Terminalia chebula* belongs to the family Combretaceae and is found throughout India especially in deciduous forests and areas of light rainfall. It is a medium to large deciduous tree; attaining a height of up to 30 m with wide spreading branches and a broad disk-shaped crown. The bark is dark-brown, often longitudinally cracked; the leaves are ovate or elliptic with a pair of large glands at the top of the petiole; the flowers are yellowish white. Fruit is green when unripe and yellowish grey when ripe.

As per Hindu mythology, it is believed that when Indra (king of dieties in Hindu mythology) was drinking nectar in heaven, a drop of the fluid fell on the earth and produced Haritaki. It is widely used in various traditional medicine systems like Ayurveda, Homeopathic, Siddha, Unani etc.

**Chemical Constituents**

*T. chebula* contains various phytoconstituents like tannins, flavonoids, sterols, amino acids, fructose, resin, fixed oils; however, it is fairly rich in different types of tannins (approximately 32% tannin content). Tannin content of *T. chebula* largely depends on its geographic conditions.

The tannins of *T. chebula* are of pyrogallol (hydrolysable) type. It contains 14 components of hydrolysable tannins (gallic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl-β-D-glucose, 1,6-di-o-galloyl-D-glucose, casuarinin, 3,4,6-tri-o-galloyl-D-glucose, terchebulin).
Other phytochemicals like anthraquinones, ethaedioic acid, sennoside, 4, 2, 4- chebulyl-d-glucopyranose, terpinenes and terpinenols have also been reported to be present \(^{119,120}\). Triterpenoids and their glycosides have been isolated from stem bark of *T. chebula* \(^{121}\). Various fatty acids were isolated from *T. chebula* and palmitic acid, linoleic acid and oleic acid were main constituents \(^{122}\). Polyphenols such as punicalin, punicalagin, terflavins B, C, and D were found in the leaves \(^{118,123,124}\). The plant is also found to contain phloroglucinol and pyrogallol, along with phenolic acids such as caffeic, ferulic, p-coumaric and vanillic acids \(^{125}\).

**Structure of compounds present in *Terminalia chebula***

![Pyrogallol](image1.png)

![Gallic acid](image2.png)

![Ellagic acid](image3.png)

![Chebulagic acid](image4.png)

![Chebulinic acid](image5.png)
Punicalagin

1, 2, 3, 4, 6-penta-O-galloyl-β-D-glucose

Corilagin

1, 6-di-o-galloyl-D-glucose

Punicalin

Casuarinin
Biological and Pharmacological properties

Different extracts of *T. chebula* exhibit antibacterial activity against a number of bacterial species \(^{126}\). Ethanedioic acid and ellagic acid isolated from butanol fraction of *T. chebula* fruit extract had strong antibacterial activity against intestinal bacteria, *Clostridium perfingens* and *Escherichia coli* \(^{127}\). Ripe seeds of *T. chebula* also showed strong antibacterial activity against *S. aureus* \(^{128}\). A strong antibacterial activity against multidrug-resistant uropathogenic *E.coli* was exhibited by ethanol extract of *T. chebula* and phenolics were found to be responsible for this antibacterial activity \(^{129,130}\).

High TPC (total phenolic content) was found in the leaves and fruits of *T. arjuna*, *T. bellerica*, *T. chebula* and *T. muelleri* and showed significantly antioxidant activity \(^{131}\). Study on antioxidation activity indicates that *T. chebula* fruits have potent antioxidative and protective effects against in vitro free radical generation and t-BHP-induced oxidative hepatotoxicity in rat primary cultured hepatocytes and rat liver \(^{132}\).

Hot water extract of *T. chebula* exhibited anti-herpes simplex virus (HSV) activity *in vivo* and anti-cytomegalovirus (CMV) activity both *in vitro* and *in vivo* in a study. These herbs may be beneficial for the prophylaxis of CMV diseases in immunocompromised patients \(^{133}\).

Recent studies indicated that acetone extract of *T. chebula* has emerged as a new alternative to treat pandemic swine influenza A infection due to its low cost, easy preparation and potential effect \(^{134}\). It has been reported that acetone extract of *T. chebula* contain various phytochemicals with promising anticarcinogenic and antimutagenic properties \(^{135}\).

Tannin extracts from dried immature fruits of *Terminalia chebula* *Fructus* *Retz.* can promote cutaneous wound healing in rats, probably resulting from a powerful antibacterial and angiogenic activity of the extracts \(^{136}\).
The chloroform extract of seeds of *T. chebula* caused dose-dependent reduction in blood glucose of diabetic rats and comparable with that of standard drug, glibenclamide in short term study. It also produced significant reduction in blood glucose in long term study. Significant renoprotective activity is observed in *T. chebula* treated rats. Thus this study clearly indicated a significant antidiabetic and renoprotective effects with the chloroform extract of *T. chebula*.

The aqueous fruit extract of *Terminalia chebula* has been investigated for its effect on cell-mediated and humoral components of the immune system in mice. Administration of *T. chebula* extract produced an increase in humoral antibody (HA) titer and delayed-type hypersensitivity (DTH) in mice. So it was concluded that extract of fruit of *T. chebula* has promising immunostimulant properties.

**Medicinal and other Uses**

*Terminalia chebula* is widely used in ayurveda, homeopathic and unani medicine system due to the wide spectrum of pharmacological activities associated with the biologically active chemicals present in this plant. It is used for the treatment of number of diseases like cancer, paralysis, cardio vascular diseases, ulcers, leprosy, arthritis, gout, epilepsy etc. The dried ripe fruit *T. chebula* has widely been used in the treatment of asthma, sore throat, vomiting, hiccough, bleeding, piles, diarrhea and bladder diseases.

It is a mild, safe and effective laxative in traditional medicine. T. chebula is an active ingredient of the well known herbal preparation, Triphala, which is used for the treatment of enlarged liver, stomach disorders and pain in eyes. According to *Sushrut-Samhita*, “Triphala” is useful in the treatment of cough, pitta, diabetes, ailments of eyes, skin diseases, intermittent fevers and indigestion.
2.2 Antibiotics

2.2.1 Amoxicillin

Amoxicillin is semi-synthetic drug and belongs to class of antibiotics called the Penicillin (β-lactam antibiotic). It is effective against various infections which are caused by wide range of Gram-positive and Gram-negative bacteria in both human and animals. It is useful in treatment of certain bacterial infections such as bronchitis, pneumonia, gonorrhea and infections of the ears, nose, throat, skin and urinary tract. It is also used in combination with other medications to eliminate *H. pylori*, a bacterium that causes ulcers.

Amoxicillin inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell wall by binding to one or more of the penicillin-binding proteins, thus inhibiting cell wall biosynthesis resulting in the disintegration of bacterial cell (bacterial lysis). Amoxicillin is susceptible to degradation by β-lactamase-producing bacteria, which are resistant to a narrow spectrum of β-lactam antibiotics, such as penicillin and due to this reason; it is often combined with clavulanic acid, a β-lactamase inhibitor. This increases effectiveness by reducing its susceptibility to β-lactamase resistance. Amoxicillin show high absorption after oral administration and this is not altered by the concomitant ingestion with food. It is commercially available is the form of capsules and tablets and also available in the form of suspensions. Common side effects of amoxicillin are nausea, vomiting and lower gastro-intestinal irritation reactions. Other uncommon adverse effects includes dizziness, headache etc.

Structure of Amoxicillin is as follows:

![Structure of Amoxicillin](image)
2.2.2 Ceftazidime

Ceftazidime is a new third generation cephalosporin antibiotic. It has a broad spectrum of in vitro activity against Gram-positive and Gram-negative aerobic bacteria, is particularly active against Enterobacteriaceae (including ß-lactamase-positive strains) and is resistant to hydrolysis by most ß-lactamases. It is well recognized widely as an ‘alternative drug’ specifically for the management and treatment of hospital-acquired Gram-negative infections. It is extensively used in the treatment of bone and joint infections, CNS-infections, gynecological infections, lower respiratory tract infections, septicemia, skin and urinary tract infections. Ceftazidime is the treatment of choice for severe melioidosis (infection with the gram-negative bacterium Burkholderia pseudomallei).

Ceftazidime exerts its action by interfering with bacterial cell-wall synthesis and division by binding to cell wall and thus causing cell death. Ceftazidime is generally well tolerated. The most commonly reported side effects are diarrhea, fever, skin rashes, transient eosinophilia and reversible elevation of liver function tests.

Ceftazidime is administered parenterally, is completely absorbed after intramuscular injection. It is white to cream coloured crystalline powder.

Structure of Ceftazidime is as follows:
2.2.3 Ciprofloxacin

Ciprofloxacin is a second generation fluoroquinolone antibiotic with a broad spectrum of antibacterial activity \(^{153}\). It is effective against a wide variety of gram-negative and gram-positive organisms \(^{154}\). Ciprofloxacin is effective in the treatment of a wide variety of infections includes skin and bone infections, gastrointestinal infections caused by multi-resistant organisms, lower respiratory tract infections, acute urinary-tract infections, sexually transmitted diseases (gonorrhea and chancroid) and multidrug resistant tuberculosis. Ciprofloxacin is recognized as a ‘drug of first choice’ in the treatment of typhoid fever \(^{149, 155}\).

The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials \(^{156}\). Ciprofloxacin promotes breakage of double-stranded DNA in susceptible organisms and inhibits DNA gyrase, which is essential in reproduction of bacterial DNA \(^{157}\).

The most common adverse effects of ciprofloxacin involve the gastro-intestinal system and usually comprise nausea, vomiting, diarrhoea and abdominal discomfort. CNS effects are seen in 1-4% of patients but are usually minor dizziness or mild headache only. Hypersensitivity reactions, most commonly skin rashes or pruritus, affect about 1% of patients \(^{158}\).

Structure of Ciprofloxacin is as follows:
2.2.4 Erythromycin

Erythromycin is a group of drugs called macrolide antibiotic and it is produced by the actinomycete species, *Streptomyces erythreus* 159. It is highly effective against group A β-hemolytic streptococci and *Streptococcus pneumoniae*. Most strains of other β-hemolytic streptococci, including groups B, C, F, and G, are also susceptible to erythromycin. Most methicillin-sensitive clinical isolates of *Staphylococcus aureus* are sensitive to erythromycin. Erythromycin has consistent and useful activity against gram-negative bacteria such as *Neisseria meningitidis*, *N. gonorrhoeae*, and *Bordetella pertussis* 160.

Erythromycin is used for the treatment of upper respiratory tract and skin and soft tissue infections caused by susceptible organisms, especially in the penicillin-allergic patient 161, 162. It is also recommended for the treatment of Sexually Transmitted Diseases like syphilis and useful in Legionnaire's disease 163. Erythromycin inhibits protein synthesis by its effect on ribosome function 164. It acts by binding the 50S ribosomal sub-unit and inhibiting translocation of the elongated peptide from one binding site to another on the ribosome thus inhibiting the addition of amino acids to the growing peptide chain 165.

Structure of erythromycin consists of a macrocyclic 14-membered lactone ring attached to two sugar moieties (a neutral sugar, cladinose, and an amino sugar, desosamine) 161. It is a crystalline, colourless compound which is slightly soluble in water but dissolves in most of the common organic solvents 166.

Structure of Erythromycin is as follows:
2.2.5 Amphotericin B

Amphotericin B is polyene macrolide antifungal agent and it plays a major role in the treatment of systemic fungal infections, in spite of the introduction of newer agents such as the azoles. It has a broad spectrum activity and it is effective against number of fungal infections including aspergillosis, blastomycosis, candidosis, cryptococcosis, coccidioidomycosis, extracutaneous sporotrichosis, mucormycosis and also in some case of hyalohyphomycosis, phaeohyphomycosis. It is topically used for treatment of external ocular infections.

Amphotericin B exhibits its activity by binding to sterols in the fungal cell wall and altering membrane permeability (creates pores in the membrane), thereby allowing the leakage of cytoplasmic components which eventually leads to cell death.

Adverse effects of amphotericin B are fever, shaking chills, and hypotension. It produces renal injury (severe kidney toxicity) by a variety of mechanisms. It is considered to be the drug of choice for many systemic, life-threatening fungal infections even with its toxicity. Its principal chronic adverse effect is nephrotoxicity and it is serious drawback to the use of this drug since its introduction. Amphotericin B has very little solubility in aqueous solutions in its pure form and so complexing with some other agent is required for clinical administration. The first such agent used was sodium deoxycholate that contains sodium phosphates as buffers. It has poor oral absorption pattern. It is available in the form of mixture, lozenges and ointment.

Structure of Amphotericin B is as follows:
2.2.6 Fluconazole

Fluconazole is a bis-triazole antifungal agent and used in the treatment and prevention of superficial and systemic fungal infections. *Candida albicans* is responsible for most fungal infections in humans and fluconazole is first-line management option for the treatment and prophylaxis of localized and systemic *C. albicans* infections. It is used in treatment of infections of the vagina, mouth and throat. It is effective in the treatment of oropharyngeal candidiasis in patients with cancer and in patients infected with the human immunodeficiency virus. Fluconazole penetrates the cerebrospinal fluid well and is approved for primary and suppressive therapy of cryptococcal meningitis in AIDS patients.

Fluconazole exerts its effect by blocking the synthesis of ergosterol which is an essential component of the fungal cell membrane. It inhibits 14-α-demethylase, a cytochrome P-450 enzyme that is necessary for synthesizing ergosterol. 14-α-demethylase converts lanosterol to ergosterol. Without ergosterol, 14 alpha-methyl sterols increase which subsequently causes the fungal cell membrane to exhibit increased cellular permeability. This causes the components inside the cell to leak.

Fluconazole has generally been well tolerated. Common adverse effects of fluconazole are nausea, headache, skin rash, abdominal pain, vomiting and diarrhea. It is a white to off-white crystalline powder.

Structure of Fluconazole is as follows:
2.3 Combination Therapy: Interaction of plant extract and antibiotics

Numbers of diseases are caused by various microorganisms in the human beings. There are various ways to treat different types of infectious diseases. Plant provides number of chemicals with antimicrobial activities. Plant based medicines are used for treatment of wide varieties of diseases for thousands of years. The plant kingdom is a valuable source of potential drugs and in the recent years there has been an increasing awareness about the importance of medicinal plants. Drugs from the plants are easily available, less expensive, safe, and efficient and rarely have side effects. 

Antibiotics are widely used to fight against various bacterial diseases all over the world. The wide use of antibiotics in the treatment of bacterial infections has led to the emergence and spread of resistant strains. It is required to find out alternative way for treatment of bacterial infections. There are various strategies to treat infectious diseases. One strategy is the use of plant extracts individually and/or as an alternative approach is the use of combination of antibiotics with plant extracts. Combination of antibiotics with plant extracts against resistant bacteria will have different mechanisms of action. The synergistic effect from the combination of antibiotics with plant extracts against resistant bacteria may lead to new ways for the treatment of infectious diseases. Some studies have found that the efficacy of antimicrobial agents can be improved by combining them with crude plant extracts against different pathogens and a number of compounds with an in vitro activity of reducing the minimum inhibitory concentrations (MICs) of antibiotics against resistant organisms have been isolated from plants.

Combination of plant extract and antibiotics are novel concepts. Studies on interactions of plant extract and antibiotics are reported and few examples are described bellow:

Purushotham, K. G., et al. carried out in vitro antibacterial activity of methanol extract of tectona grandis leaves with tetracycline. The MIC was carried out for Tetracycline alone and then for the methanolic extract of Tectona grandis and finally combination of tetracycline and methanolic extract of Tectona grandis . The MIC values were found to be
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less with tetracycline alone and it was found to be still lesser with the methanolic extract of *Tectona grandis*. However, the MIC was found to be the least with combination of tetracycline and methanolic extract of *Tectona grandis*. Moreover, the therapeutic efficacy was found to be higher even in low concentration. This clearly exhibits the advantages of administering the combinations of tetracycline and methanolic extract of *Tectona grandis* over the other two individual forms coupled with enhanced synergistic activity 187.

Adwan, G., & Mhanna, M investigated *in vitro* interaction between water extracts of *Psidium guajava*, *Rosmarinus officinalis*, *Salvia fruticosa*, *Majorana syriaca*, *Ocimum basilicum*, *Syzygium aromaticum*, *Laurus nobilis* and *Rosa damascena* and antimicrobial agents like oxytetracycline HCl, gentamicin sulfatecell, penicillin G, cephalaxin, sulfadimethoxine as sodium; and enrofloxacin using both well-diffusion and microdilution method. The results of this experiments using well-diffusion method demonstrate that these plants showed *in vitro* interactions between antimicrobial agents and plant extracts were additive against the five strains of *S. aureus*, while using microdilution method showed synergistic effects between combination of antibiotics and plant extracts with significant reduction in the MICs of the test antibiotics against these strains of *S. aureus* 188.

Souto de Oliveira et al. investigated the synergistic activity of norfloxacin, tetracycline and erythromycin with ethanol extract of *Mangifera indica* L. peel against *S. aureus* strains. Extract did not display significant antibacterial activity individually (MIC = 2048 µg/ml), but it modulated the activity of antibiotics (MIC = 512 µg/ml), i.e. in combination with antibiotics, a four-fold reduction in the MIC values for tetracycline and erythromycin was observed. The study indicated that mango peel could serve as a source of potential adjuvant of antibiotics, which adds value to this mango by-product 189.

Cynanchum stauntonii (Schltr) against two different strains of Staphylococcus aureus was carried out by Yang, Zai-Chang, et al. Paederia scandens/penicillin or ceftriaxone combinations, Taraxacum monticulum/penicillin or ceftriaxone combinations, showed a powerful bactericidal activity to two strains of S. aureus. Cynanchum stauntonii combined only with gentamicin showed antimicrobial activity. Isatis tinctoria, Scutellaria baicalensis, Rheum palmatum can improve the antimicrobial activity of four antibiotics 190.

Olajuyigbe, O. O., & Afolayan, A. J. investigated the effect of interactions between methanolic extract of Acacia mearnsii and eight antibiotics (Erythromycin, Tetracycline, Metronidazole, Amoxicillin, Ciprofloxacin, Nalidixic acid, Chloramphenicol, and Kanamycin) by agar diffusion and checkerboard assays. The synergistic interactions indicated that the bactericidal potentials of the antibacterial agents were improved and combining natural products with antibiotic could be potential sources for resistance-modifying agents useful against infectious multi-drug resistant bacteria 191.

Isogai, Emiko, et al. studied the synergistic effects of Japanese green tea extract and levofoxacin against enterohemorrhagic Escherichia coli infection in a gnotobiotic mouse model. Mice fed on JGTE conferred a significant degree of protection against an oral challenge with enterohemorrhagic Escherichia coli. However, complete elimination of the bacteria from the mice was difficult. The combination of Japanese green tea extract and levofoxacin increased the survival rate and reduced damage to target organs. Thus, dietary supplementation with green tea extract improved the therapeutic effects of antibiotic treatment 192.

Ofokansi, K. C., et al. evaluated antibacterial activities of the combined leaf extract of Phyllanthus muellerianus and Ciprofloxacin against Urogenital Isolates of Staphylococcus aureus. The combined extract or methanol fraction with the standard drug, ciprofloxacin, produced synergistic effect in many of the combination ratios against the test organism and this has a lot of therapeutic implications in the treatment of infections caused by S. aureus 193.
Synergistic effect of *salvadora persica* extracts, tetracycline and penicillin against *Staphylococcus aureus* was carried out by Ahmed, Z., et al. Tetracycline and Penicillin showed zone of inhibition 23.0 mm and 18.0 mm respectively. Leaf and Stem extract of *salvadora persica* showed 10.5 mm and 18.0 mm respectively. Zone of inhibition (ZOI) was increased to 30.0 mm in case of combination of tetracycline and leaf extract of *salvadora persica*. Combination of Tetracycline and stem extract of *salvadora persica* exhibited 31.5 mm. ZOI of combination of penicillin and stem extract of *salvadora persica* was observed 21.0 mm. This study proved the synergistic effect between plant extracts and antibiotics and it could be beneficial against *S aureus*.

Stefanović, O. D., evaluated synergistic activity of *Salvia officinalis* and *Cichorium intybus* extracts and commonly used antibiotics, amoxicillin and chloramphenicol. Combinations of acetone and ethyl acetate extracts of *S. officinalis* and *C. intybus* with antibiotics inhibited the growth of tested bacteria at a lower concentration than when the single drugs were tested separately. There was a synergistic or additive for the most of the tested strains. It was found that the presence of sub-inhibitory concentrations (between 1/4 MIC to 1/32 MIC) of the acetone extract modulated the activity of amoxicillin by reducing the concentration of antibiotic needed to inhibit the growth of bacteria. This study indicated the potential of *S. officinalis* as a source of antibiotic resistance modifying compounds.

Fadli, Mariam, et al. evaluated the antibacterial effect of the association between conventional antibiotics (ciprofloxacin, gentamicin, pristinamycin, and cefixime) and essential oils of endemic Moroccan thyme species, *Thymus maroccanus* and *T. broussonetii*, on antibiotic-resistant bacteria involved in nosocomial infections. Eighty combinations of essential oils and antibiotics were tested. Out of these combinations, 71% showed total synergism, 20% had partial synergistic interaction and 9% showed no effect. Carvacrol, the major constituent of T. maroccanus and T. broussonetii exhibited also an interesting synergistic effect in combination with ciprofloxacin.
Zain al-abdeen, et al. evaluated the interaction of aqueous garlic extract and two antibiotics, and ampicillin against some multi-resistant bacteria. The synergism effect of the aqueous garlic extract and two antibiotics ciprofloxacin and ampicillin was carried out by using double disc diffusion method. Synergism was not observed between ampicillin and the garlic extracts, while the ciprofloxacin with garlic extract showed synergism effect in some bacterial isolates.\(^{197}\)

Stefanović, Olgica, and Ljiljana Comic investigated synergistic antibacterial interaction between ethanol, ethyl acetate and water extract of \textit{Melissa officinalis} and five commonly used antibiotics (streptomycin, chloramphenicol, tetracycline, amoxicillin, rifamycin) by disc diffusion method. The water, ethanol and ethyl acetate extracts of \textit{M. officinalis} enhance the activities of amoxicillin, streptomycin, tetracycline and chloramphenicol. Synergistic activity with antibiotics was demonstrated even that the sub-inhibitory concentrations of extracts were used. The observed enhancement of antibiotic activity could be explained by the presence of biologically active compounds in these extracts.\(^{198}\)

Giordani, Roger, et al. tested the in vitro susceptibility of \textit{Candida albicans} to ketoconazole and \textit{Euphorbia characias} latex alone or in combination using the macrobroth dilution method. The MIC 80% of crude latex and ketoconazole are respectively 159 μg protein/ml and 0.3901 μg/ml. The utilization of a mixture of latex at several concentrations (7.8–15.62–31.25–62.5 and 125 μg protein/ml) and ketoconazole indicates a synergistic effect between latex and ketoconazole.\(^{199}\)

Shin, S., & Lim, S. determined the effects of herbal essential oils on \textit{Trichophyton} spp. growth and the effects of \textit{Pelargonium graveolens} oil and its main components citronellol and geraniol combined with ketoconazole against \textit{Trichophyton} spp. (\textit{T. schoenleinii}, \textit{T. erinacei} and \textit{T. soudanense}). Combination of the essential oil fraction of \textit{P. graveolens} and its main components, geraniol and citronellol, exhibited strong synergism with ketoconazole against \textit{T. schoenleinii} and \textit{T. soudanense}, with fractional inhibitory concentration (FIC) indices in the range of 0.18–0.38.\(^{200}\)
Braga, L. C., et al. evaluated the interaction between *Punica granatum* (pomegranate) methanolic extract and antibiotics against 30 clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) by use of the broth dilution method. Methanol extract of *Punica granatum* (pomegranate) had a significant effect on improving antibiotic efficacy when combined with ampicillin, chloramphenicol, oxacillin, and tetracycline, whereas in combination with gentamicin it proved to be less efficient. These combinations offer an alternative for the extension of the useful lifetime of these antibiotics.

Khan, M. S. A., & Ahmad, I. carried out antifungal activity of essential oils and their synergy with fluconazole against drug-resistant strains of *Aspergillus fumigatus* and *Trichophyton rubrum*. All test combinations showed synergistic interactions against the test strains except the oils of *C. martini* and geraniol against *A. fumigatus*. Cinnamaldehyde showed strongest synergy with fluconazole against *A. fumigatus* and *T. rubrum* by reducing the minimum inhibitory concentration of fluconazole up to 8-fold.

Giordani, R., et al. investigated the antifungal activity of the essential oil from *Cinnamomum cassia*, alone or combined with amphotericin B. A decrease of the MIC 80% of amphotericin B was obtained when the culture medium contained essential oil concentrations ranging from 0.08 to 0.1 μL/mL. The strongest decrease (70%) was obtained when the medium contained 0.1 μL/mL of essential oil. This potentiation of amphotericin B obtained in vitro may show promise for the development of less toxic and more effective therapies especially for the treatment of HIV infection. The potentiation of the antifungal effect of amphotericin B by this oil can be used for the treatment of candidiasis.

Moon, S. E., et al. investigated Synergistic effect between clove oil and its major compounds and antibiotics (ampicillin and gentamicin) against oral bacteria. As a result of the combination of clove oil or eugenol with antibiotics, the MIC and MBC were reduced to one half-one sixteenth. This combination could be employed against cariogenic and periodontopathogenic bacteria.
Sakharkar, Meena K., et al. carried out interaction of antibiotics and phytochemicals against Pseudomonas aeruginosa. The MIC of sulfadiazine was 256 µg/mL, and of gentamicin was 2 µg/mL. Combination of gentamicin with one-quarter the MIC of caffeic acid reduced the MIC of gentamicin 4-fold. When sulfadiazine was tested with one-quarter the MIC of protocatechuic acid, quercetin, and caffeic acid, the MIC was reduced 4-fold in combination with each of the drugs. A result of this study indicates the potential efficacy of photochemical in combination with antibiotics for enhancing total biological activity\(^\text{205}\).

Stefanovic, Olgica, et al. investigated antibacterial activity of *aegopodium podagraria* L. extracts and interaction between ethanol extracts and two antibiotics, streptomycin and chloramphenicol. The activity of streptomycin and chloramphenicol was increased 8-fold and 10-fold, respectively against *Bacillus subtilis*\(^\text{206}\).

Interaction of clotrimazole and cinnamon oil was evaluated for synergistic assay using Checkerboard method by Abdel-Aziz M. M. The interaction between clotrimazole and cinnamon oil against twelve of multi-drug resistant dermatophytic isolates *in vitro* revealed that this interaction was synergistic or in-additive while antagonism was not detected; the interaction was synergistic in the most isolates while in additive was demonstrated in only one isolate\(^\text{207}\).

Okoye, C. O. B., et al carried out study on Synergistic effect of jatropha curcas root extract and ampicillin on staphylococcus aureus and escherichia coli isolated from clinical specimens. The extract in combination with ampicillin in the ratios of 1:1, 1:4, 2:3 and 3:7 showed synergistic effects and indicated higher zones of growth inhibition for *Staphylococcus aureus* with higher values of 21.25 mm, 23.00 mm, 25.20 mm and 28.00 mm respectively\(^\text{208}\).
2.4 References


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