Chapter 2

REVIEW OF LITERATURE
2. REVIEW OF LITERATURE

2.1. *Careya arborea*

*Careya* is genus of myrtles and named in the honor of Dr W. Carey, who was an Indian botanist and updated the edition of Roxburgh’s flora indica. The genus *Careya* comprises of angiosperms first described as a genus in 1819 (Roxburgh, William. 1819. Plants of the Coast of Coromandel 3: 13) and chiefly three species (Kew world checklist of selected plant families) have been found depending on their geographical status are *Careya arborea* Roxb. (From Afghanistan to Singapore), *Careya herbacea* Roxb.- (India, Nepal, Bhutan, Bangladesh) and *Careya valida* Kurz - Andaman Islands (Hanelt, 1979). The plants of this genus are mostly trees and are found in India along with one species that occur in North Australia. The leaves are stalked and obviate, flowers are large but sessile of bright colors like red, yellow and greenish giving rise to spike or corymbose type of inflorescence.

The vascular plants of the genus consist of different families (*Kubitzki, 2004*) and the clade is cleaved into three families: the Napoleonaeaceae (*Prance*, 2004), Scytopetalaceae (*Tsou, 1994b; Appel, 1996, 2004) and the Lecythidaceae (*Prance and Mori, 2004*). The later one contain about 20-25 genera and 250-300 species of woody plants which are distributed in tropical South America and Madagascar. Lecythidaceae is a monophyletic group in the Ericales (*Morton et al., 1997; Anderberg et al., 2002; Schonenberger et al., 2005*). The Lecythidaceae and its associates comprise of a pantropical clade of trees (*Mori, 2004*). Lecythidaceae by Mori et al., (2007), have subfamilies as:

✓ Foetidioideae
✓ Planchonioideae
✓ Lecythidoideae
✓ Napoleonaeoideae

These subfamilies encompasses numerous genera like Planchonioideae which consist of Abdulmajidia, Grias Barringtonia, Chydenanthus, Petersianthus, Planchonia; the genus Allantoma, Careya,, Gustavia, Cariniana, Bertholletia,
Corythophora, Couratari, Couroupita, Eschweilera, Lecythis is placed under Lecythidoideae. Foetidioideae carries genera Foetidia and Napoleonaeoideae which consists of Asteranthos, Crateranthus, Napoleonaea (Prance and Mori, 1979). The new world Lecythidaceae sweep from Veracruz, Mexico to Paraguay and the great diversity and solidity of trees of the Brazil nut family (Lecythidaceae) are found in Amazonia (Mori et al., 2001). Among 277,069 trees from across Amazonia and that Eschweilera, the genus with the most species in Lecythidaceae, is represented by more trees than in any other genus of plants in Amazonia (Steege et al., 2006) and is positioned as the third most abundant family.

Tsou (1994a) carried out an embryological study and suggested that Lecythidoideae and Planchonioideae form the fundamental group of Lecythidaceae, whereas Foetidioideae and Napoleonaeoideae should be kept apart from it and identified as separate families. Lecythidaceae were formerly kept close to Myrtaceae due to their partitioned petals, and distinct syncarpous inferior ovary with axile placentation (Miers, 1874) and numerous stamens. However, later on it is distinguished from Myrtales as the arrangement of leaves is dissimilar; number of unicellular ovules is also contradictory. Moreover, intraxylary phloem and vented pits were absent in wood a sequence of embryological feature (Prance and Mori, 1979).

Careya arborea Roxb is a member of Lecythidaceae family and is found in different tropical areas of the world like India, Sri Lanka and Malaya peninsula (Karunakar et al., 1997; Kedare et al., 1953). In Ayurveda it is known as “Kumbhi”, on account of the hollow on the upper part of the fruit giving its appearance identical to a water-pot; “Kavalumara” in Kannada and “Wild guava” in English (Gurudeva, 2001). Puta-tanni-maram is the tamil name meaning "water-bark-tree" in allusion to the exudation trickling down the bark in dry weather. The tree is familiar as Ka Li Yu Rui in China (Zhou et al., 2011). The plant is endowed from Afghanistan, Andaman Islands, India, Myanmar and in northern Peninsular Malaysia.
Fig. 2.1: *Careya arborea* tree

It can be cultivated from seeds, roots and stumps in cropping years. The trees prefer a well-drained soil which may be both alluvial soils and loams. It also occurs on latiritic soils and trees requires sunny locations and do not perform well in shade. Additionally the tree also prefers a well-drained, sandy or even rocky soil. In India the annual diameter increment can be up to 0.5 cm, but growth of coppice is faster, 0.6 - 0.9 cm in diameter for 8-year-old coppice shoots ([http://www.worldagroforestry.org](http://www.worldagroforestry.org)). This tree is highly fire resistant and seeds are slightly poisonous whereas fruit is edible.

2.2. **Taxonomical profile**

Kingdom: Plantae  
Phylum: Tracheobionta  
Division: Magnoliophyta  
Class: Magnoliopsida  
Order: Lecythidales  
Family: Lecythidaceae  
Subfamily: Planchoniodeae  
Genus: Careya  
Species: *Careya arborea* Roxb
2.3. Morphology

*Careya arborea* is medium sized deciduous tree with height about 20 m. with handsome spreading crown and is propagated by seed. It is the only Malesian species, which is found almost throughout the range of the genus, but in Peninsular Malaysia it is found in the northwest and occurs rarely.

![Fig. 2.2: Stem bark of *Careya arborea*](image1)

Surface of bark is fissured and dark grey in colour while inner bark is red and fibrous. Bark is uneven, coarse, stony, manifesting shallow cracks, exfoliating in small flakes having no odour but astringent taste.

![Fig. 2.3: Leaves of *Careya arborea*](image2)
Leaves are simple, green coloured, broadly obovate, tapering towards base, stipulated and margin is crenate; lateral nerves 10-12 pairs, parallel, prominent, intercostae reticulate, prominent, tertiary veins oblique; petiole is 0-1.8 cm, long, stout and margined thickly arranged at the terminals of branches, penninerved, and non-dotted having red colour when young. The colourful leaves (turns red in cold season) and rapid growth features of the tree is suitable for growing it as ornamental plant.

![Fig. 2.4: Flower of Careya arborea](image)

Inflorescence is terminal and raceme. It blossoms during March-April. Flowers are large showy bisexual, yellowish green with red purple stamens, unpleasant odour, arranged in 1-10 flowered inflorescences, calyx and petals are free and 4-4 in number, many stamens, inferior ovary, multilocular with plenty of ovules arranged in 2 series, style is one. Filaments equaling or slighting exceeding the petals, connate into a tube at the base, the innermost and outermost rows usually without anthers; anthers versatile, dehiscing longitudinally.
Fig. 2.5: Seeds of *Careya arborea*

Seeds are 1.5-2 cm long and 1 cm wide having dark brown colour, indehiscent and exalbuminous. Shape of seeds ranges from oval to ellipsoid with hard testa and are wrinkled. They have pleasant odour and astringent taste (*Anonyms*).

Fig. 2.6: Fruits of *Careya arborea*

Fruit is drupe, 5-7.5 cm in diameter, greenish in colour, globose to depressed globose, crowned by sepals and style and containing several seeds. Fruits get matured in May. There is large embryo in seeds and obsolete cotyledons residing in fleshy pulp (*Parrotta et al.*, 2001). The seedlings have hypogaeal germination in which seed contain only swollen hypocotyls cotyledons are missing.
2.4. Common Names

(http://www.flowersofindia.net/catalog/slides/Wild%20Guava.html)

- English - Wild Guava, Ceylon Oak, Patana Oak
- Hindi - Kumbhi
- Marathi - Kumbha
- Tamil - Peezhai, , Puta-tanni-maram
- Malayalam - Peelam, Pela, Paer, Alam
- Telugu - araya, budatadadimma
- Kannada - alagavvele, daddal
- Bengali - Vakamba, Kumhi, Kumbhi
- Khasi - KaMahir, SohKundur
- Assamese - Godhajam, kumara
- Sanskrit - Bhadrendrani, Sinhala Kahata

(http://www.instituteofayurveda.org/plants/plants)

2.5. Microscopy of leaf

Transverse section of the leaf passing through midrib region shows the presence of thin walled epidermis with rectangular cells on both adaxial and abaxial surface of the leaf. The epidermis was covered by a thin layer of cuticle followed by collenchymatous ground tissue. Palisade cell is single layered; midrib region show one median vascular bundle which has large size and two lateral vascular bundle. Vascular bundles are covered with fibrous bundle sheath. One group of sclerenchyma is present at upper side above the median vascular bundle. Xylem is arranged in cup shaped and surrounded by phloem facing toward the lower side. Lateral vascular bundle also shows sclerenchymatous bundle sheath which encircles the vascular bundle. Careya arborea leaf surface shows the anisocytic arrangement of stomata which is characteristic of Lecthyidaceae.

2.6. Microscopy of seed

Seed in the transverse section display that testa is composed of sclerenchymatous cells, which are chased by a layer of collapsed cells of outer integument. Cuticle is present on both the sides of interior integument. On its superficial surface dark brown material is present. The cotyledon of the seed is incorporated with thin
walled, parenchymatous cells having polygonal shape. These cells are arranged in many layers and replenished with extensively starch grains and intermittently with oil cells (Ayurvedic Pharmacopoeia of India). Powder microscopy of the seeds revealed cotyledonous cells in several fragments, plentiful starch grains. The size of starch grains is around 5 µ and having simple and spherical shape. The microscopy also exhibits the stone cells of testa scattered throughout.

2.7. Ethnomedical uses

Numerous segments of the tree are casted in ayurvedic formulations to tackle a number of ailments like cough and other respiratory disorders, worms, diarrhea, ulcers and fever. The traditional use of bark of Careya arborea is to treat tumors, bronchitis, as astringent, antidote to snake venom and skin diseases. In addition, the bark also find useful as demulcent, alexiteric, expectorant, anthelmintic, antipyretic and antipruritic (Kumar et al., 2008) and in different conditions such as toothache, wounds, catarrh, dyspepsia, colic, haemorrhoids, diarrhea and dysentery, skin problems, epilepsy, abscesses, eruptive fever particularly smallpox (Kelland, 2005) and as tonic after childbirth (The Wealth of India 1992; Nadkarni, 1998; Kirtikar, 1991; Rastogi, 1969). Juice of bark is taken in inflammation associated with cough and cold (Naik, 2014) and joint pain (Sahu, 2010). Paste of flowers of C. arborea and fruits of Terminalia chebula and Emblica officinalis, prepared by macerating in ghee, and is taken orally in empty stomach to treat infertility (Mahishi, 2005).

The plant was reported to be used for safe abortion of unwanted pregnancy. It is used as fish poison for catching fish easily (Natesan, 2007). It is an important ingredient of polyherbal formulation ‘Jigrine’ which is helpful for the treatment of hepatic disorders in the Unani system of medicine (Karunakar, 1997). Leaves are used in treatment of dislocated bones, (Harsha, 2005) body aches, myalgia, (http://indianmedcinalherbs.blogspot.in) and rheumatic pain (Seraj et al., 2013). Poultice of leaves is applied to obstinate ulcers for 3 to 4 times a day rapidly. A paste from leaves is applied on the face to reduce the swellings, (Alawa, 2012) skin diseases (Murthy, 2012) and tongue ulcer (Chandra, 1985).
The grounded bark is grinded and mixed with salt, applied externally for the treatment of foot and mouth disease of cattle (Devi Prasad, 2014). In veterinary medicines it is also used to treat corneal opacity (Rajakumar, 2016), paste of bark in curd is used to overcome weakness in cattle (Mallik, 2016). In Ayurvedic system of medicine various parts of the tree are known as padmaka. Bark, leaf and fruits are used as thermogenic and lowers the fever, also in colic, intestinal worms, and healing of vaginal ruptures (Pradhan, 2014). Fruits are edible, aromatic, (Negi, 1994) and are used for worship in Indian festivals like Mahashivratri. Powdered fruits are used to shatter overweight and its pulp is applied to scalp for hair growth. The decoction of stem bark is taken in empty stomach for 7 days and is beneficial in pile treatment (Rout, 2009).

2.8. Pharmacological studies

The methanolic extract of Careya arborea stem bark was found to have potent hepatoprotective and antioxidant activities (Manthey, 2001) and exhibit CNS depressant action Swiss albino mice and Wistar albino rats (Kumar, 2005).

It was reported that the methanolic extract Careya arborea (bark) possess anticoagulant activity via assay of activated partial thromboplastin time (aPTT), Prothrombin time (PT), and thrombin time (TT). It was shown that bark extract caused significant increase \((p<0.05)\) in aPTT, PT and TT at all doses and results were comparable with warfarin (Subhadradevi, 2010).

The anticancer potential of methanolic extract of bark against Dalton’s lymphoma ascites and solid tumors was demonstrated by Natesan et al. There is remarkable decrease in percent inoculation when methanolic extract of the bark is given by oral route to mice for 10 days at the dose of 250 or 500 mg/kg body weight. Whereas when the extract was administered \(i.p.\) in the range of 5 - 25 mg/kg body weight for 14 days showed an immense reduction in the solid tumor volume caused by DLA cells (Rosangkima, 2004).

Diarrhea induced in mice by using castor oil was significantly reduced by methanolic extract of stem bark and favors the traditional use of the plant as anti-diarrheal (Saha, 2003).
The methanol extract of *Careya arborea* possessed significant increase in hypnotic effect generated by the phenobarbitone, in Swiss albino mice (20–25 g) and Wistar albino rats (150–180 g) of any sex (*Ramanathan Sambath, 2008*).

Ethanol (70%) extracts at dose of 300 and 600 mg/kg, reveals significant antiulcer action. This study was carried on Wister rats of either sex originated by ethanol cold stress and pyloric ligation models (*Kumar, 2013*).

Koya tribes of Pakhal in Andhra Pradesh practice the plants in ethnoveterinary. The bark (*Careya arborea*) is also used to cure debility in cattle’s. Tribal people make a paste by crushing the bark with curd and administer orally to cattle to treat severe debility (*Murthy et al., 2007*). More oversome tribes of Kerala used decoction of leaf of *Careya arborea* Roxb as antidysentric drug and also in diarrhea. Flower (calyx) contains mucilage and act as demulcent, decoction of fruit is used to improve digestion (*Tessy et al., 2011*).

The antioxidant and hypolipidemic activity of a polyherbal formulation *Kumbhajatu* contains *Careya arborea* (*Ghosh et al., 2010*) as one of its ingredient and studied in hypercholesterolemic rats. The powdered form of *Kumbhajatu* fed as diet supplement in the range of 250 to 500 mg/kg to hypercholesterolemic rats showed remarkable reduction in plasma lipid profiles and elevated levels of catalase, hepatic superoxide dismutase (SOD), and glutathione. Whereas levels of malondialdehyde, cholesterol, triglycerides, low density lipoproteins and very low density lipoproteins in both the groups were significantly decreased.

Lather *et al* (2011) reviewed pharmacological potential of the plant used in the treatment of piles. A large proportion of population suffers from piles and many indigenous drugs have been used in India for many decades for its treatment. An exhaustive summary of medicinal plants useful in piles is given, in which *Careya arborea* is also enlisted as one of the useful plant.

Ahmad *et al* (2002) reported analgesic principles from the bark of *Careya arborea*. An alkaloid piperine is separated by bioactivity guided isolation from the bark of *Careya arborea* an experiment was conducted and it is found that the compound betrayed 41% and 53% inhibition in acetic acid induced writhing in mice, when administered orally (20 and 30 mg/kg body weight). Moreover at the
same doses the compound exhibited 31.8 and 52.4% prolongation of tail flicking time in mice by 30 min when treated with radiant heat method.

*Careya arborea* leaves and flowers are promulgated to be used in paste form to cure several skin diseases (*Solomon, 2004*). Syrups and wines made from ripe fruits used as sedatives. Seeds are edible and quench thirst.

Hepatoprotective profile of *Jigrine*, a polyherbal pharmaceutical dosage form containing aqueous extract of about fourteen medicinal plants inclusive of *Careya arborea* Roxb as one of its components has been reported (*Ahmad et al.*, 2002). Thiocetamide induced liver damage rats were fed orally with 0.5 ml/kg/day for 3 weeks and evaluated for hepatoprotective potential of *Jigrine*. The biochemical parameters (like AST, ALT in serum; TBARS and glutathione in tissues) were observed to evaluate hepatic chores. The study suggested the administration of *Jigrine* to thioacetamide induced hepatotoxicity rats showed hepatoprotective activity.

The methanol extract of *Careya arborea* root possesses antifertility effects in Albino mice. A strong antifertility effect was revealed in mice after giving treatment of the methanol root extract for a period of 14 days and was found severely affected estrous cyclicity in normal adult cyclic mice (*Kalita et al.*, 2011). Haloi *et al* found reversible anti-fertility activity in adult female Albino mice with methanol root extract of *Careya arborea* by reduction in number of mature graffian follicles & corpora lutea and degeneration of corpus luteum with persistent haemorrhage.

Krishnaraju *et al* (2005) studied bioactivity of Indian medicinal plants using *Artemia salina*. Lethality assay which represents an easy and fast bioassay for testing bioactivity of plant extracts, and correlates with cytotoxic and antitumour properties. It was observed that, the water extract of flowers of *Careya arborea* possess drastic cytotoxicity with LC50 >5,000μg/ml.

Wadkar *et al* (2008) suggested that methanol extract of the leaves of plant is favourable as an acid base indicator in acid base titrations and encouraging results were obtained because it gives sharp change in colour against
phenolphthalein (standard synthetic indicators) at the equivalence point during titration.

Elhag et al (2011) investigated carbon tetrachloride treated group of animals in which increased levels of serum AST, ALT, ALP and bilirubin were shown whereas there is reduction in haematological parameters like Hb, PCV, RBC, and MCSH.

Antioxidant and alpha-glucosidase inhibitory properties of Vietnamese edible plants were investigated by Mai et al (2007) and interrelationships with polyphenols were evaluated. Among these plants Careya arborea showed high α-glucosidase inhibitory activity of 67% at dose of 0.8 mg lyophilized material pemillilitre solution and remarkable antioxidant activity at concentration of 30 μg lyophilized material/ml solution.

2.9. **Phytochemical constituents**

Bark of the Careya arborea chiefly showed the presence of steroids, terpenoids, (Mahati, 1973; Ramachandra, 1976; Das, 1982) alkaloids, flavonoids (Gupt, 1975) and saponins, (Gedeon, 1956) tannins, (Kulakkattolickal, 1987) Pyroligenous acid and other components (Kedare, 1953) maslinic acid the chief constituents present in it are terpenoids, flavonoids, alkaloids, saponins and tannins (Wadkar, 2008).

The other main constituents present in stem bark of C. arborea Roxb are β-sitosterol, lupeol, betulin, betulinic acid, 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl] piperidine (bark) (Yoganarasimhan, 1996). Moreover triterpenoid lactones I named careyagenolide as well as and 2α-hydroxyursolic acid were also reported (Das, 1982).

Triterpenoid saponin, arborenin and desacylescin III are separated from the methanol extract of the leaves of Careya arborea by bioguided-fractionation by Mandal et al (Kulakkattolickal, 1987). It also has treasure of alkaloid piperine, (Ahmed et al., 2002) sapogenin, (Kincl, 1957) taraxerol, (Mahato, 1967) arborenin,
desacylescincIII, *(Mandal et al., 2006)* sapogenols, careyagenolide, maslinic acid and 2α-hydroxyursolic acid.

The plant also carry 2α,3β-dihydroxytaraxastan-28, 20β-olide, *(Das, 1982)* α-spinasterol; α-spinasterone, baringtogenol-C and careyagenol-E *(Mahato, 1972)*. Bark contains lupeol and botulin. Leaf contains ellagic acid, hexacosanol, quercetin, β-sitosterol, β-spinasterol, taraxerol and taraxeryl acetate, valoneic acid, careaborin, β-amyrin; α-spinasterol *(Khare, 2007)* is present in seeds.

Fruit are reported to have dihydroxybenzoic acid (gallic acid, kaempferol 3-O glucopyranoside, quercetin 3-O-glucopyranoside, quercetin 3-O-(6-O-glucopyranosyl)-glucopyranoside, *(Ariyaratna, 2007)* and careaborin *(Talapatra, 1981)*.

Behera *et al* (2012) extracted leaf of *Careya arborea* in solvents of different polarity and subjected the same to phytochemical analysis. The presence of various phytoconstituents like tannins, flavonoids, terpenoids, cardiac glycosides, saponins, anthraquinones, sterols and phytosterols was observed. HPTLC analysis revealed that, leaves extracted by ethyl acetate, methanol and water contain flavonoids.
Betulin

Betulinic acid

Piperine

Taraxerol

Maslinic acid

2-hydroxyursolic acid
Fig. 2.7: Structures of some phytoconstituents present in *Careya arborea*

2.10. Marketed formulations

- Kumbhajatu Ayurveda Rasashala, treat hyperlipidemia (*Ghosh, 2010*).
- Jigrine Hamdard Laboratories, treat liver problems (*Kumar, 2013; Najmi, 2005*).
- Habb-E-Kabid Naushadri Hamdard Laboratories treat liver disorders ([http://buyherbalgoodhakeemcom/habb-e-kabinaushadrihamdard](http://buyherbalgoodhakeemcom/habb-e-kabinaushadrihamdard)).
• Hamdard Ghutti Hamdard Laboratories, a paediatric preparation used to treat constipation of newborn and infants (Jelliffe, 1988).

2.11. Role of natural products in anti-cancer drug development

Drugs derived from natural sources are used in medicine from the antiquity. The most fruitful strategy for the discovery of novel drugs is the use of natural products. Natural products from different source like terrestrial plants, vertebrates and invertebrates and microorganisms, marine organisms (Newman et al., 2000) played supreme role in every part of the world in treating and arresting human diseases. A number of reviews and reports reflected the importance of Natural product in modern medicine (Newman et al., 2003; Koehn, 2005; Paterson, 2005; Balunas, 2005; Jones, 2006).

Plant based system played an essential role in primary healthcare by repairing and strengthening body systems, by boosting immunity and destroying mortifying pathogens without side effects. World Health Organization estimates that around 65% of the human population makes use of plant drugs in their primary health care (Farnsworth, 1985). Herbal medicine is an integral part in indigenous systems of traditional medicine like Ayurvedic, homeopathic, naturopathic. Besides customary values, phytomedicine also hold great public and medical interest ubiquitously as provenance of novel lead compounds for drug discoveries.

Extraction and characterization of several active phyto-compounds from these green factories have given birth to high activity profile drugs. The potential active anti-cancer drugs like vinca and taxol can be best examples (Huie et al., 2002). Medicinal plants being the most successful source of drugs and have a great contribution in anti-cancer drug design and development. The scientific era started in late 1960s when Hartwell and co-workers established the role of podophyllotoxin and its by-products as anticancer agents. The discovery of camptothecin (CPT, 1) with inhibition of DNA topoisomerase-1 as unique mode of action as an anticancer drug provided a new hope to the field of chemotherapy (Srivastava et al., 2005).
Taxol (Paclitaxel as generic name and taxol, (24) as trade name is obtained from the pacific yew Taxus brevifolia is a complex polyoxygenated diterpenoid. The other important natural products in the drug discovery include antimalarial drugs like artemisinin and the anticancer agent’s vinblastine (25) and vincristine (26). There are different strategies which have been employed nowadays to acquire compounds for drug discovery from various sources which include isolation of phyto-constituents from plants and related natural sources; combinatorial chemistry; synthetic chemistry; high throughput screening; and molecular modeling. Irrespective of these latest interests or advancements, medicinal plants or natural sources still remains an important source of lead molecules in drug discovery process (Balunas, 2005).

![Chemical Structures](image)

Coumarins and its derivatives were implicated as promising anticancer compounds. Many anti-cancer agents have been isolated from various plant sources Podophyllum species (lignans derivatives etoposide (27) and teniposide (28) (Allen et al., 2005; Choi et al., 2008). Camptotheca acuminata irinotecan and topotecan (Cragg et al., 1994; Cragg et al., 1993; Wang, 1998) and many others. It has been reported (Meghalaya and Mizoram, 2004) that most of modern drugs being used clinically are of natural origin. Among them many have been recognized to be capable of
inducing apoptosis in different cancer cells of human origin. A number of bioactive natural products possess heterocyclic chemical moieties which have played an indispensable role in the drug discovery process (Tanaka, 2009).

Cheliensisine (29) belongs to oxepinochromone class and is obtained from *Goniothalamus cheliensis* (Annonaceae) has potential antineoplastic activity (Gu, 2000). Davallioside A (30) and its 1″-epimer Davallioside B are present in the rhizomes of *Davalia mariesii* in Davalliaceae family to treat stomach cancer (Cui, 1990). Rohitukine (31) is a chromone alkaloid derived from the leaves and stems of *Amooraro hituka* cytotoxicity against human HL-60 promyelocytic leukemia and HCT-116 colon cancer cells (Ismail, 2009).

Steroidal plant hormones namely Brassinosteroids are promising leads for potential anticancer drugs (Malikova et al., 2007). Natural brassinosteroid 28-homocatasterone (32) and 24-epibrassinolide (33) showed strong action in growth inhibition in G₁ phase of cell cycle and induce apoptosis. They also concomitant reductions in the percentages of cells in the S phase (Malikova et al., 2008) in MCF-7 breast and prostate cell lines. Nimbolide (34) a triterpenoid derived from the flowers of *Melia azadirachta* holds antiproliferative activity against few cancer cell lines (Roy et al., 2007). Some plants exert their anticancer effect through quenching - reactive oxygen species (Arulkumaran et al., 2006) like nut milk extract of *Semecarpus anacardium* Linn.
CHAPTER-2

REVIEW OF LITERATURE

![Chemical Structures](image-url)
Colchicine (35) an alkaloid isolated from poisonous meadow saffron plant (*Colchicum autumnale L.*) acts by distorting tubulin/microtubule equilibrium and halting mitosis in the metaphase (*Russo et al.*, 2004; *Ohkanda et al.*, 2002). Combretastatins, a class of compounds originally derived from the African willow tree, *Combretum caffrum*, are powerful reversible inhibitors of tubulin polymerization by binding to the colchicine binding site of tubulin. The most active of these compounds are combretastatin A-4 (36) and combretastatin A-1 (37) (*Haluska*, 2002).

Many of the anticancer drugs interacting with DNA may act via DNA-enzyme complex or by targeting rare paranemic DNA structures. Some of the chromone derivatives act by interacting with DNA and inhibiting the topoisomerase activity, such as psorospermin (38) and its synthetic analogues (39-42) (*Hurley*, 2001; *Bocian et al.*, 2006).
Chromone derivatives (43-46) show significant anticancer activity by competitive inhibition of over-expressed protein tyrosine kinases; (Hardcastle et al., 2005) these kinases act like switches by catalyzing the transfer of g-phosphate of either ATP or GTP to specific tyrosine residue in protein substrates; their elevated expression contributes to the transformed state of cells in many human malignancies.

EGCG (Epigallocatechin gallate) is the most abundant catechin compound which is beneficial in the treatment of brain (Das et al., 2010), prostate (Hsieh, 2009), cervical (Qiao et al., 2009), and bladder (Philips, 2009) cancers. Epigallocatechin gallate binds to anti-apoptotic protein Bcl-xl and inhibits (Leone et al., 2003), a protein which helps in survival of both cancer and normal cells (Cherbonnel-Lasserre, 1997). They suppress the AOM-induced colonic pre-malignant lesions (Shimizu et al., 2008), interfered with EGFR
signaling (Adachi et al., 2009), and inhibits HGF (hepatocyte growth factor)-induced cell proliferation in human colon cancer cells (Larsen et al., 2010). Inhibitory action of mitogen-activated protein kinases (MAPK), cyclin-dependent kinases, growth factor-related cell signaling, activation of activator protein 1 and NF-κB, topoisomerase I and matrix metalloproteinase is also induced by the EGCG.

The exploration and establishment of bioactive anticancer drugs leads to the recognition of diverse terpenoids that hamper the metastasis and proliferation of cancer cells through different channels. Terpenes are organic hydrocarbons produced by a variety of plants, and when denatured by oxidation is referred to as terpenoids. Terpenes play an unbelievable fundamental role in plants with natural protection from microorganisms, insects, and other environmental stresses. Structurally, terpenoids have several subclasses, like monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, and tetraterpenoids. Chemical structures of about 2500 terpenoids with potential practical applications in the fragrance and flavor industries, and in particular pharmaceutical and chemical industries (Gershenzon, 2007) are investigated.

An escalation of cancer via metastasis represents one of the terrible jeopardy for the cancer (Liabakk, 1996). The production of certain matrix metalloproteinases (MMPs) shows resemblance with cancer invasion/metastasis in various forms of cancer like breast, liver, colon, lung and ovarian (Lin, 2001). It was also reported that the secretion of MMP-2 and -9 from A431 cells is stimulated by EGF, while the same is suppressed by luteolin and quercetin (Hertog, 1993). Consequently, agents that inhibit EGFR tyrosine kinase activity may have potential in the prevention of tumor metastasis. Endogenous inhibitors such as 2-macroglobulin, and the tissue inhibitors of metalloproteinases (Chambers, 1997) causes inhibition of MMPs in vivo. The tumor invasion essentially involves the secretion of MMPs, as indicated by the observations that treatment with antibodies or inhibitors against MMPs abolished the invasive behavior of certain tumor cells (Rhee, 2002; Liotta, 1992). Therefore, one would expect to limit the metastatic potential of cancer cells by the suppression of the secretion and of the action of the activated MMPs in cancers. Some flavonoids, like luteolin, quercetin and apigenin, could inhibit MMP-2 and -9 activities (Ende, 2004) and it is believed that an inhibitory effect of
these flavonoids on MMP-2 and -9 is increased by the addition of number of hydroxyl groups.

Cantharidin from *Mylabris phalerata* has been used as an anti-cancer agent for the treatment of hepatoma and esophageal carcinoma (*Liu, 2009*). The proceedings of purified catalytic subunits of PP1 and PP2A are retarded at a sub micromolar level by catharidin (*Honkanen, 1993*). The inhibition PP2A by cantharidin provokes cancer cell apoptosis in an IKKa/IkBa/ p65 NF-κB pathway-dependent manner, leading to eventual activation of TNF-a, TRAILR1, and TRAILR2 extrinsic apoptotic signaling (*Li W, et al., 2011*). Furthermore, the mitogen-activated protein kinases (MAPKs)/ERK/JNK/ p38 signaling axis was also found to be tangled in cantharidin-triggered apoptosis in cancer cells (*Li W, et al., 2010*).

Triptolide is extracted from the root of *Tripterygium wilfordii* (*Hook, 2007*) a known Chinese herb. Triptolide halts cell growth at slighter concentrations and instigate apoptosis at elevated concentration (*Kiviharju, 2002*). The inhibition of proteasome-mediated NF-κB pathway is responsible for its anti-proliferation activity. Triptolide inhibited the trans-activation of NF-κB induced by TNF-α and also blocked NF-κB-mediated induction of the inhibitor of apoptosis c-IAP1 and c-IAP2 (*Lee et al., 1999*). It has also inhibited NF-κB trans-activation without inhibiting nuclear NF-κB DNA binding activity (*Jiang et al., 2001*) and increased its binding activity (*Qiu et al., 1999*). Besides that mRNA de novo synthesis is also inhibited by inhibiting RNA polymerase I and II (*Vispe et al., 2009*).

Flavonoids constitute human diet and are present in foods commonly as O-glycosides with sugars attached at C3 position. Flavonoids are plant secondary metabolites, benzopyran derivatives (phenyl substituted chromones) carrying a wide range of therapeutically effects and disclose the beneficial effect for humans in addition to anti-cancer activities. They are believed to thwart with the progression of cancer by reconstructing divergent enzymes and receptors in signal transduction pathways that are involved in cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis. The activities of cellular protein tyrosine kinases are harmonized and thus the growth of malignant cells was obstructed by flavonoids, therefore they have remarkable implications in security against cancer (*Huang et al., 1999; Lee et al., 2002; Akiyama et
al., 1987). Also the modulating effects of flavonoids on the cell cycle (Sato et al., 1994) and apoptosis (Wei et al., 1994; Kyle et al., 1997) are conceivably factors that can mediate their anti-proliferative activity. Moreover, the possible anti-metastatic properties of flavonoids, includes suppression of the secretion of MMPs (Huang et al., 1999; Lee et al., 2002) and the modification of epithelial cell migration (Lee et al., 2004) which could also be relevant reason to their anticancer action. Quercetin, a poly-hydroxylated flavonoid and exerted its potent inhibitory effects on growth of malignant tumor. The antiproliferative effects are synergistic in combination with cisplatin, due to inhibition of PKC (Hoffman et al., 1989).

Lignans are natural products of two phenylpropanoid (C6-C3) units although their oligomers have also been known. Antitumor activities of lignans are also important. Two lignan lactones of the dibenzocyclooctadiene class, known as steganacin and steganagin, have significant cytotoxic effect both in vivo and in vitro. These compounds have been obtained from an alcoholic extract of the South African tree Steganothaenia araliaceae (Umbelliferae) (Kupchan, 1964).