CHAPTER – II

REVIEW OF LITERATURE

A literature review involves the systematic identification, location, scrutiny and summary of written articles that contain information on research problem (Polit and Humpler 1978). In order to broaden understanding and get insight into the various aspects of infertility an overview on both research and non-research related literature was the viewed from published articles as well as from internet.

According to (Morin-Davy 1998) infertility is the inability to conceive within 12 months of sexual relation without the use of contraception, or carry to a live birth a pregnancy.

Menning (1997) described infertility as a developmental crisis that can threaten a couple’s future goal. Shapiro, (1982) stated that the consequence of infertility as a harsh and unexpected shock.

2.1. Prevalence of infertility

The World Health Organization (WHO) estimates that worldwide 60-80 million couple suffer from infertility (WHO 2004). Infertility is estimated to affect 8-12% of couples worldwide and varies across region of the world. Infertility may be due to unknown or unpreventable conditions. The WHO 2004 estimates the primary infertility in India to be between 3.9 and 16.8% overall. The data on prevalence of infertility in India is very less. Among Indian states the infertility rate varies from 3.7% in UP, Himachal Pradesh and Maharashtra to 5% in AP and 15% in Kashmir. The existence of 10 infertility vary across tribes and castes of similar areas in India.
Types of infertility

Infertility is classified into primary and secondary infertility. WHO defines infertility as the ‘Inability to conceive within 2 years of exposure to pregnancy among women 15-47 years old. Globally most couple suffer from primary infertility. If they are unable to conceive after giving birth to first child it is referred to as secondary infertility.

Statistics on infertility

Based on the census reports of India (2011-2014) childlessness has risen by 50%. A survey according to India Institution of Population Studies Mumbai (2010). Out of 250 million individuals 13 to 19 million couple are likely to be infertile.

The findings of Boivin Bunting (2007) showed that prevalence of infertility in developed and developing countries ranged from 3.5% to 17% in developed countries and 7% to 9% in developing countries. The mean was found to be 9% in this study out of million women who are currently interfere would wide, medical treatment is sought by 60% by (Kumar 2007).

Data collected through framed interview schedule of 1305, Khairwarde tribes showed the prevalence of infertility and its socio economic factors in tribal communities of central India. Study showed that female infertility was 14% and it is higher in Khairwar tribes than non-Khairwar tribe.

The study conducted by Larsen (2000) in less developed countries (28 countries in sub Saharan Africa, China, Chile & India) showed that the prevalence of life time infertility ranged from 5 to 25.7%. The lowest estimated rate of childlessness in the first 5-8 yrs of marriage was 1.3% in China. The highest
estimated rate was 16.4% to sub Saharan African countries. 8-28% was the range of infertility for the 28 countries. Moshin Awardy (2001).

Newton et al., (1999) stated that though infertility is basically a medical conditions it affects the emotional activities of the couple and they report a number of stressors. The stress may be related to their sexual functioning, stress related to their endurance and their relationship with the family members and outsiders.

2.2. Psychosocial dimensions

Psychopathological response is not seen in all infertile patients. Recent review concluded that not all patients suffer from stress. (Grcil 1997). Newton et al (1990) Beaurepaire et al., (1994) stated that infertile individuals undergoing assisted conception show frustration if the treatment is not a success.


Based on the census reports of India (2011-2001-1991-198) childlessness has risen by 50%. Out of 250 million individuals estimated to be attempting parenthood 13 to 19 million couple are found to be infertile according to a survey of Indian Institution of Population Studies Mumbai (2010).

According to a study conducted by Naeimeh Tayebi (2009) in Iran, to assess the degree of sexual dysfunction among infertile women and its correlation with age,
duration of marriage and cause of infertility after diagnosis of infertility it revealed high rate of sexual dysfunction.

Kelly Weeder (2006) observed that 2 million couples in the United States are infertile in his study on the impact of life style risk factors on female infertility in USA.

Moray Norma (2002) showed that excess fat in the abdominal area is overall connected to disorders of reproductive system. Obesity and overweight are serious and prevalent conditions in western country and causing health effect including reproductive dysfunctions.

**Primary and secondary infertility**

Study conducted by Mohsin (2001) among rural women in Egypt on 10 and 20 infertility including some risk factors revealed that the prevalence of infertility was 10.4% overall. In the study 7.9% reported 20 infertility and 2.5% reported 1\(^{o}\) infertility. Secondary fertility increases with age and prevalence of fertility was higher among women under 30. Woman who were married under the age of 16 and these above 30 were observed to have both types of infertility.

Pasch and Christensec (2000) stated that there are drawbacks in social scientific research on infertility and enlisted them as small sample size, poor sampling methods, use of non standardized methods, lack of adequate control samples and suggested that the studies rely mainly on self reported data.

**Impact of infertility**

Shireen jejbhowy (1998) studied the levels, patterns, consequences for social scientific research on infertility in India. Globally it affects 50-80 million couple.
Infertility has been disregarded as both a health issue as well as a topic for social science research in South Asia. The consequences of infertility is leading to marital instability, low self-esteem, harrasment and negative attitudes [incidence or prevalence]

The stress levels in infertility were assessed biochemically as well as questionnaire based. Median baseline, follicular phase and pre-operative serum PRL (229, 311 and 45 μm1U/l) Cortisol 278, 369 and (496 n mole / l) and state anxiety score (38, 40 and 49) respectively all increased during simulated 1vf treatment on comparison with control group. The study was conducted by Harlow et al (1995) and it suggested that anxiety levels are greatest in IVF treatment.

Due to instability in the lives of couples with infertility there are several adverse effects. A case-control study has reported that amongst infertile women the rate of remarriage is 3.5 times higher (Jamayev, et al 2012).

2.3. Common factors for infertility

Among the female problems the common factors for infertility are evaluating dysfunction (40%) tubal and infertine (40%), and unusual problems such as atomic, genetic or auto immune (20%) and unexplained infertility (20%) are the research findings by Speroff, case cited in Angard (1999) (Scott and Hofmann 1995) states that the literature consistently demonstrates the value of diminished ovarian reserve screening. Ovarian reserve screening identified women with greatly diminished chances of getting pregnant. Clinicians are urged to validate the threshold values with the assay system used in their own lab before the application of these tests as the screening tests consists of clomiphene citrate challenge test based on day 3FSH
Menstrual cycle: luteal phase and follicular phase

REPRODUCTION AND EMBRYONIC DEVELOPMENT

• REPRODUCTIVE ANATOMY OF THE HUMAN FEMALE
measurement and the GnRH against stimulation. The predicted value of an abnormal test for failing to conceive are very high. Nestler et al., In Majority of cases the reason for infertility were unknown. Variety of malfunctions in male and female were responsible for infertility.

Patel Mital et al., (2012) exam noted the proportion of various factors for infertility valuation problem, endometriosis, tubal factor, uterine problem in females and low sperm count, sperm morphology and motility in males.

Pasquali et al., (2007) increased risk of miscarriage and decreased effectiveness of ART in women ovulatory and menstrual dysfunction is seen in obese women and in obese men it is associated with decreased androgen production and erectile dysfunction.

The two most important factors influencing the probability of conceiving without medical invention in unexplained fertility is age and the other is duration of trying for pregnancy as identified by Templton (1995).

Zinges and Dorfman observed the social and environmental factors responsible for infertility. It is seen that professionals high group delay conception by use of contraceptive which makes them vulnerable to infertility including ageing and stress. Farmers and other class of people who are not professionals are exposed to pesticides and harmful chemicals hence face infertility. Alcohol consumption and use of tobacco has effect on decreasing fertility.

2.4. Biological factors

Eskenazi et al., (2003) observed that a cross-sectional study is necessary to relate between age and semen quality as it is an important criteria for fertility status.
As it is clear about the effect of maternal age on fertility and it is unclear whether paternal age also effects fertility.

Excess fat is strongly related to disorders of reproductive system. Moderate weight less and abdominal fat reduction helps to improve menstrual cycle. Overweight and obesity are serious and prevalent conditions in western countries leading to reproductive dysfunction (Moray and Norman (2002)).

Complete metabolic, hormonal, clinical and psycho-social data were obtained from a total of 120 women into PCOS. PCOS had been shown to cause a reduction in quality of life, psychosocial well being and sexual satisfaction according to a study conducted by Hahn et al., (2005).

Kolstad et al., (1999) conducted a follow up study to characterize how the menstrual cycle pattern relates to fertility. Main finding was the probability of pregnancy occurring within one menstrual cycle. The mechanisms of the present findings probably are female functional disturbances in implantation or sustained pregnancy, linked with mental cycle length, conception, ovulation. Thus recognition of environmental and medical causes of abnormal menstrual cycle patterns may provide clues to the cause of infertility.

Exercise induced menstrual irregularities appears to be multifactorial in origin and remains a diagnosis of most cases are reversible with diet and exercise modifications. Search was performed to review the related articles from 1996 to 1998 to provide an overview of exercise induced reproduction of dysfunction of an approach to evaluation and management by Chen and Brozyski (1999).
2.5. Management of infertility

Demyttanaere et al., (1994) conducted a study in 40 women undergoing IVF to assess their personality characteristics, psycho endocrinological stress response and outcome of IVF. They were divided into 2 subgroups 17 with normal menstrual cycles and 23 women with subtle disturbances or luteal phase insufficiency. The study revealed a correlation of the state anxiety level of the patient in the early follicular phase with negative outcome in IVF is seen in women with subtle cycle. The results reveal that subtle cycle disturbance or IVF syndrome or Luteal phase insufficiency and endometriosis could the associated with psycho endocrinological stress levels.

Chemicals

The first fertility drug of choice for women with irregular menstrual cycles is clomiphene citrate. Clomiphene is mild and stimulates the pituitary to produce FSH and LH, it boosts the follicle growth and release of the egg. It is less expensive and the risk for multiple births is lower than with other drug. Other side effects of clomiphene are 5% of getting twins, ovarian cysts, nausia, headache, weight gain and slight chance for miscarriage.

Gonodotrophin

Include various types that contain a combination of FSH and LH or only FSH. Gonodotrophin directly stimulate the ovaries to produce multiple follicle. Whereas clomiphene works indirectly by stimulating the pituitary gland to secrete FSH. Gonodotrophins include menotropins, hcg, FSH and GnRH they prevent the premature release of the eggs for ART.
PLATE – 4

Anterior pituitary Hormones

- Neurosecretory cell
- Blood vessel
- Releasing hormones from hypothalamus
- Endocrine cells of the anterior pituitary

Pituitary hormones:

- TSH
- ACTH
- FSH and LH
- Growth hormone (GH)
- Prolactin (PRL)
- Endorphins

Targets:

- Thyroid
- Adrenal cortex
- Testes or ovaries
- Entire body
- Mammary glands (in mammals)
- Pain receptors in the brain

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How does sexual reproduction occur?

- Two sources of DNA
  - **Gametes** are special sex cells that contain half of a set of DNA
    - **Sperm**: made by the male
    - **Egg**: made by the female
  - **Fertilization** is when the sperm and the egg join together
**Treatment for ovarian failure**

In PCOS laser surgery or fertility drugs can be used. In overweight and glucose intolerance melformin can be administered. GnRH replacement is done in case of absence of GnRH. In case of premature ovarian failure Assisted Replacement Therapy (ART) is given and in luteal phase defect hormone replacement with or without fertility drug is the treatment.

Ovulation is regulated by hormone activity. 20 to 30% of female fertility is due to ovulatory problems. Mechanical obstruction like adhesive, scar tissue and blockage affect the fallopian tubes and uterine cavity can prevent fertilization and implantation. It accounts for 25-40% of the female infertility problems. Mostly the PID (Pelvic Inflammatory disease) and endometriosis occur under mechanical obstruction for PID to avoid infectious disease like venereal disease the best treatment is to seek diagnostic tests and get the bacterial infections treated with antibiotics. Scarring and damage can be treated by laser surgery to remove scar tissue and repair the areas.

For endometriosis the abnormal growth can be shrunk by drug or surgery can be done to remove them. Upto 10-15% of the female infertility is due to cervix, fallopian tubes and the uterus. Upto 15% is due to cervix and of a small % is due to uterus. Drugs can cure cervical mucus problems. Fibroids can be removed by laser treatment.
2.6. Alternate systems

1. Herbal

    Of overall fertility 35-40% account for female infertility. Ayurvedic treatment for overlation disorder is treated by herbs like Harmal (Paganum harmala), Dashnool (Ten roots) Asoka (saraca india) and others.

    For blocked fallopian tubes, adhesions and Pelvic Inflammatory Disease (PID) Triphala, Kutki and punarava are given. For women who are under weight and have a small underdeveloped cervix or uterus Gokshur (Tribulus terrestis) Bringraj (Eclipta alba) Bharangi (Derdendrum serriatum) and Manjistha are the herbs.

2. Homeopathy treatment

Fibroids and polyps

    A sudden rise in estrogen levels causes a hormonal imbalance and causes fibroids. Fibroids are muscular growth in the uterine cavity which is benign. It hinders the implantation of the egg and growth of the embryo. Some homeopathy remedies restore fertility.


PCOS

    The homeopathic remedies can be very useful in stimulating the ovaries when taken during the first 14 days of menstrual cycle for those who are suffering from PIOS because they rarely ovulate. The homeopathy remedies like Lilium tigrinum 6C, seccio aureus 3X, Agnus castus 3X and folliculinum can be taken.
**Ovaries**

Based on the type of disturbance the remedy can be selected. Following are the formulations like Apis Mellifica, secale, Bryta muriatica, Lachesis, Colocyntis, Lycopodium and Borase.

**Endometriosis**

Endometriosis is a condition where the endomaterial lining migrates to areas beyond the nitrus causing bleeding of those areas where hormones stimulate and cause contraction of the tissues. The lining can extend to abdominal cavity, the fallopian tubes and borvels. This can affect fertility and hence homeopathy can help in restoring fertility treatment include antoxilum fraxineum, apis, medorrhinum, Folliculinim TC, Lachests, Nux.Vomica, Pulsatilla, Sepia and others.

When patients undergo laproscopy for treatment of infertility the following homeopathi medicine help to heal the wound faster. Calendula 30C, 200C Bellins perennis 30C 300C. Arnica 200C Carbo vegetabilis 30C, 200C and phosphorous.

**3. Natural system of treatment**

**Yoga**

There are features that have been specifically developed to improve the reproductive health of the individual hereby increasing the chance of setting pregnant. Both male and female can benefit by yoga for fertility and minimise stress which ultimately balances the hormones promoting the ability to conceive and maintain their mental health. Hatha Yoga, Kripalu Yoga, couples yoga help infertility.
**Naturopathy**

The naturopathic multidimensional system that includes several areas to check health and help fertility as well. The methods are diet, exercise, yoga, acupuncture, herbal medicine, aromatherapy, homeopathy massage.

Naturopathy medicine is tailored to suit our individuals specific needs. This aims to improve the overall health by increasing immunity, and giving resistance to infections and illness.

**Flower remedies**

Thought it is considered sacred to offer flowers to god in temple there is or hidden traditional remedy to mankind. Fresh flowers of various floral essence infusion and aroma kindles our mind and we feel relaxed when entering into the temple.

Flower remedies are readily available and they can be taken on their own in a mix of your our selection. 3 to 4 drops can be added to a glass full of water not more than 7 drops. Simple essences are sold and it is known as stock. It can be diluted and taken.

Flowers like sheOak reduces stress caused by infertility and also improves hormonal imbalance. Noni reduces the negative feelings and fosters feelings of nurturing, while chestnut also promotes positive thinking. Wisteria promotes calmness. Aspen helps to reduce feelings of anticipation and anxiety, thus reducing stress.
Aromatherapy helps us to relax reducing the level of stress and depression. Aromatherapy assists in regulating the menstrual cycle and promoting a healthy reproductive system.

Essentials oils used in aromatherapy are concentrate of distilled seeds, leaves of bark help to stimulate relaxation of the muscles and to receive tension. They are very costly and available in small quantities as it is very difficult to extract and available in small amounts. The oil is a concentrate it should be applied by dilution method.

Starting from final day of the periods. Oil can be used in almond oil base or grape seed oil or wheat germ oil. In the oil burner method the essence of the oil is allowed to inhale through nestribls of boiling water and adding a fero dope of the oil. In baths the oil is added in drops to the warm water bath which reduces stress.

**Acupuncture and female fertility**

Studies show that acupuncture can be helpful on its own or conjunction is effective with assisted reproductive technology (ART) Reproductive medicine and fertility centre in Colorado found that a group of women who underwent both IVF and acupuncture for infertility 51% of them pregnant whereas only 36% of those who only underwent did. These women who received acupuncture and IVF had lesser rate of mis-carriage and still-birth.

4. Siddha

**Kapikacchu**

*Mucuna prureins* reduces oxidative damage and is a potent antiooxidant by preventing disruption in the membrane integrity of sperms [Tripathi et al.]

L-Dopa
isolated from mucuna prurein a precursor of dopamine functions as a neurotransmitter and has been shown to act as a nerve tonic [Tomita] and to promote fertility [Minu]

**Gokshura (Tribulus terrestrics)**

An active principle from the herb Gokshura (*Tribulus terrestris*) protodioscin is converted to DHEA (Dihydroxy epiandrosterone). Which improve sexual desire and sperm production as it is a precursor of hestosherone (Adimajca...) Caretta *et al* reported that Vasoactive substances like nitric oxide is stimulated by the testosterone which results in satisfactory erection.

Gokshura treatment in a study showed increased intracaverrous pressure in the penis and enhanced sexual behaviour. This is due to the release of nitric oxide in the nerve endings that innervates in the corpus cavernosum results in the blood flow in the penis and thus omprones the functioning of the musculature in this region [Gautham].

Other herbs Bala [*Sida cordifolia*] and Salammisri [*Orchis moscula*] have fertility enhancing functions. *Sida cordifolia* is mostly used in general debility, nervous disorders and sexual inadequacy. The roots of orchis mascula is tuberous and possess good nutritional value and is used as a tonic and aphrodiasic.

**Shatavari (Asparagus recemosus)**

*Asparagus racemosus* is most often used for infertility treatment in women also for threatened miscarriage, leucorrhoea and menopausal problem. It increases fertility by nourishing the ovum. The plant contains estrogen compounds. The plant is multi-branched, spinous under shrub, bearing numerous succulent and tuberous roots. The plant is demulcent approdiciac and galactagogue (it promotes the milk
secretion). The results of a study suggest estrogenic effect of the herb on the female mammary gland and genital organs. [Pandary Sri].

2.7. Traditional herbs to cure Gynaecological disorders

Herbs are used in the management of female infertility. The pharmacological actions of the herbs are beneficial. *Symplocos racemosa* (Lodhra) Lodhra normalises FSH, LH required for the normal wellbeing. *S. racemosa* showed relaxant and antispasmodic effect. It can correct menorrhea and acts as a sedative. Two alkaloids of the bark Lofurine and Colloturine are present in sufficient quantities. CCRAS, (1986).

Bala and Seshadri (1971) reported the active phytochemical cosmarins, mesuferron, mammeism and mesuanic acid. B-sitosterol and triterpenoid-guttiferol and antibiotic mesuagin oil and fatty acids (palmitic, stearic and linoleic acid) present in the herb Nagatesar (*M. ferrea*) the fruits and seeds are used for fertility treatment.

Mahee Buti (Rhus Coriara Linn) the galls of the plant contains tannins, some essential oils and tannins. Phytochem. CCRAS (1986) used to treat menorrhagia.

Kaiphal (Myrica nangi thunb) The root and bark have triterpenoid and B-sitesterol. Other chemicals are proanthocyanidin and myricanol. Other phytoconstituent, are glycosides, saponin, flavanoids, tannins and reducing sugars useful to treat gynaecological disorders. (Desai 1973).

**Semal musli (Salmalia Malabaricum Schoot & Endle)**

Phytochemical investigation of medicinal plants, CCRAS, New Delhi (1986) reported that the stem and bark have secondary metabolites triferpenoids and steroid-sitosterol. Kaemperol and quercietin have also been found the extracts have been useful in treating menorrhagia in women.
Jal Jamni (*Cocculus villosus*)

The leaves of Jal Jamni was found to contain cocuslin and biscoclaurine which contains a base component called peendulin necessary to treat menorrhagia and leucorrhea disorder in female. CCRAS (1986).

**KUTKI (P. Kurroa)**

Kutki (Picorhiza Kurroa Royle (Benth))

The biologically active constituents of the dried rhizome contains the bitter active principle Kutkin, kurrin, apocyanin, kurrim, kutikol. The glycosiders are picroside and picrohizen and kutikisterol in the steriod helpful in the treatment of menorrhagia and leucorrhea in female. (Dhar *et al.*, 1968).

**2.8. Selected herbs for the study**

**2.8.1. *Piper Nigrum***

The common Pepper or pipernigrum belongs to the family piperaceae, is a prefitable therapeutic plant. Pepper is used everywhere in the world as a part of various sauces and meat dishes. It contains major alkaloid piperine (1-peperoyl piperidine). It is mostly used as a drug in Ayurveda and Unanin medicine. Achartya *et al.*, (2012).

**Antimicrobial activity of dark pepper**

Kumar *et al.*, studied the antimicrobial action of silver nanoparticles from leaf and stem extract of piper nigrum incorporated and assessed against agrarian plant pathogen. The antimicrobial action of silver nanoparticles were demonstrated against plant pathozed. Hence this technique was a useful applicant in harvest change and assurance in the agrarian nanotechnology a developing science.
Anticancer activity of black pepper piperine is the predominant alkaloid present in the tumour development in various models. The alcoholic extract of peppercron and piperine displayed improvement of immunomolulatory and antitumour function. By changing lipid peroxidation it decreased lung disease. Selvendran and Sakthisekaran (2004).

As angiogenesis plays a key role in tumour growth piperine may be used as an inhibitor of the angiogenesis for the treatment of malignancy. Doucette et al., (2013).

**Anti-cancer activity**

The treatment for emaculation safe prostate growth FDA affirmed drug is Docetaxel (a cytotoxic chemotherapeutic specialist). This drug is detoxified in the liver by CYP3A4, and piperine is found to repress the hepatic CYP3A4 enzymatic action. The combination of docetaxel and piperine showed piperine supports the docetaxel function and it could be safe. Piperine in non-genotoxic and found to have anti-tumour effect. Makhov et al., (2012).

**Anti-inflammatory activity**

Piperine was found to have pain relieving function. Prestaglandin E2, cyclooxygenase 2, IL6 and metalloproteinase levels were analysed by ELISA and RT-PCR technique. Piperine treated rats were found to have diminished secretions of the above parameters which show that the agony and ligament manifestations have been diminished by piperine. It was presumed piperine showed analgesic functions. (Bang et al., 2009).
Antidiarrheal activity

Black pepper extract was analysed for anti-diarrheol action. 75, 180, 300mg/ was fed to rats which were previously treated with caster oil and magnesium sulfate to induce loose bowel. The G1 mobility was assessed by charcoal. The black pepper showed an enormous anti-diarrheol effect piper nigrum also showed anti-mobility. May be because of the presence of starches and alkaloids. (Shamkuwar et al., 2012).

Digestive functions

Platel and Srinivasan studied on the impact on digestive juices of intestinal mucosa in trial rats. The rats were fed with piperine which increased the functions of intestinal lipase, sucrase and maltase. In another study he showed that piperine has effect on pancreas and increased the activity of pancreatice lipase, amylase, trypsin and chymotrypsin. (Patel and Srinivasan 1996).

Anticonvulsant effect

*Invivo* anticonvulsant action of piperine was studied in pentylenetetrazole (PTZ) and picroterin (PIC) which induces seizures models of epilapsy in mice. A remarkable delay in the PTZ-PIC model was noted after peritoneal infusion of piperine at a dosage of 30, 50 and 70 mg/kg. The results reveal the anticonvulsant effect of piperine which perhaps intervened through GABAergic pathways. (Bhukari et al., 2013).

Other pharmacological action

Piper nigrum (Black pepper) or toxic free compound “piperine” shows many pharmacological functions like antihyperpensine, antiplatelets, antipyretic, antifungal,
antispasmodic, antiapoptotic, antimetastaic antimutagenic, antiasthamatic. (Ahmed et al., 2012).

2.8.2. Aloe vera

Antidiabetic effect

Water soluble fraction of Aloe specious have glucose-reducing function and some of the components modulate glucose transporter 4 MRNA expression. In his *invivo* and * invitro* studies strongly demonstrated this. *Aloe vera* gel decreased body weight, body fat and insulin resistance in obese prediabetes and early montreated diabetic patients. Devaraj et al., (2008).

Clinical study by Anand *et al*., (2010) suggested that *Aloe vera* gel may act as a safe antihyperglycemic and antihyper choolesterolemic agent for type 2 diabetic patients without any significant effects in other normal blood lipid levels. The day also found that the efficacy of aloe-emodin-8-0-glycoside isolated from the gel in enhancing glucose transport and its transformation to glycogen.

Tanaka *et al*., studied that diabetic mice chronically treated with phytosterols of *Aloe vera* gel reduced blood glucose remarkably. Shein *et al* has shown that dietary aloe formula decreases obesity induced glucose tolerance by inducing anti-inflammatory cytokines and also by suppressing inflammatory response in the white adipose tissue and liver.

Antioxidant effect

*Aloe vera* contains enormous amounts of antioxidants including α-tocopherol (vit E), ascorbic acid (vit c), carotenoids, flavanoids and tannins. Aloe gel is well known to eat-up or scavenge the free radicals. (Saini and Saini, 2011).
Rajasekaran et al., (2005) showed that there was reduction in blood glucose level in diabetic rat administered with ethanolic extract of *Aloe vera* gel which also prevent excess formation of free radicals through various biochemical pathways and reduces glycation of enzyme.

Significant correlation was established between total phenolic and antioxidant property of *Aloe vera* extracts by Kammoun et al., (2011).

**Hepatoprotective effect**

Misawa *et al.*, (2012) phytosterols isolated from *Aloe vera* could induce the upregulation of fatty acid oxidation in the liver, which favours the reduction of hyperlipidemia. Further PPAR α-ratio was decreased in diabetic treated rat.

**Anticancer activity**

Aloe-emodin (AE), a natural compound in aloe is also a subtype of anthroquinone and has varied biological functions including anticancer activity. Aloe emodin showed chemoprotective effects against 1, 2-dimethylethydrazine induces preneoplastic lesions in the color of wister rats. Hamiza *et al.*, (2014).

Recent reports have shows that aloe emodin has antiproliferation effects on some types of cancer cells, such as squamous, lungs, glioma and neuroectodermal cancer cells. Lin *et al.*, (2011).

In a study conducted on human malignant melanoma cells Lin *et al.*, 2005 reported the inhibitory effect of Aloe Emodin on the gene expression activity of N-acetyl transferase, which plays an important role in the metabolism of aryl amine carcinogens.
Antimicrobial activity

Ferro et al., (2003) has described aloe gel as an antibacterial agent. This established the susceptibility of gram-negative and gram-positive bacteria to the inner gel extract of *Aloe vera*.

The polysaccharides of aloe gel have the direct antibacterial function through the stimulation of phagocytic leucocytes to destroy bacteria. Pugh et al., (2001).

*Aloe vera* contains a chemical or a phytoconstituent which is pyrocatechol, a hydroxylated phenol it is known to have toxic effect on microorganisms. Cowan (1999).

Kametani et al., 2007 noted that *Aloe vera* consists of an active compound anthraquinone. Anthraquinone is structural analogue of tetracycline. This acts like tetracycline and inhibits the protein synthesis of bacteria by binding to the ribosomal A site (where the aminoacyl tRNA enters).

Antiviral activity

Many reports suggested that Aloe gel has antiviral properties that presents virus adsorption, attachment or entry to the root cell. Crude extract of Aloe vera gel has antiviral activity against herpes simplex virus type 2 strain was proved by an invitro study. Cellini et al., (2014). Lowther et al (2012) found that *Aloe vera* was capable of expressing human protein namely interferon alpha 2(1FN2).

Effect on estrogen status. Estrogen receptor is inhibited by a distinct mechanism which suggests a possible application of anthroquinones a metabolite of Aloe gel in preventing breast cancer. Isolated emodin and aloe- emodin from Aloe gel specifically suppress breast cancer cell proliferation by targeting estrogen receptor α protein.

**Antihyperlipidemic activity double blind**

A randomized placebo controlled clinical trial on hyperlipidemic type 2 diabetic patients the efficacy of aloe gel was checked and it reduced the levels of total cholesterol and LDL significantly. Huseini et al., 2012 Hyperlipidemia is one of the consequences that leads to a condition called poly cystic ovarian syndrome (PCOS). *Aloe vera* gel treated PCOS rats showed tremendous decrease in plasma triglyamide and LDL cholesterol levels with an increase in HDL. Maharajan et al., (2010).

Aloe has beneficial effects on the prevention of fat development and it reduces the occurrence of otherosclerosts through altering the risk factors Dana et al., (2012).

The aloe gel has phyto constituents with antihyperlipidemic effects and has shown to have effects on the management of PCOS. It also helps to revere the abnormal shows cycle, glucose intolerance and lipid metabolizing enzyme activities. Desai, et al., 2012.

**Antiulcer activity**

For the treatment of H. pylori gastric infection aloe gel is used as it acts as a natural novel effective agent. *Aloe vera* gel promotes digestion and used in the treatment of peptic ulcer. Newly formulated aloe and myrr based gel is found to be

2.8.3. Nigella Sativa

Nigella Sativum is usually known as dark seed. Nigella sativa is developed worldwide in many nations like India, Pakistan, Syria, Turkey, Middle Eastern Mediterranean area, South Europe, Saudi Arabia. This therapeutic plant belongs to the family Ranunculaceae. Nigella Sativa belongs to Southern Europe, North Africa and Southwest Asia. It is considered as a super natural herb which is religious and know for its wide range of pharmacological potential. Khare (2004) Al. Bukhari (1976) stated that it is one of the best healing pharmaceutical herb among muslims. The dark seed in solution is used for all sickness the wonder her is quoted in one of the prophetic hadith that it can cure all ailments with the exception of health. It is additionally suggested for use or general promise in Tibb-e-Nabai (prophetic medicine).

The seeds of Nigella and its oil have been used for a long time in the treatment of different diseases all through the world. it forms and important component in the Indian medicine like unani and Ayurveda. Sharma et al., (2005).

Able Salam (2012) has stated that this Nigella seeds can be used to cure wide oilments like douretics, antihypertensive, antidiabetic, anticancer immunomodulatory, analgesic, antimicrobial, antihelminthic, spasmylytic, bronchodilator, hepatoprotective, gastroprotective, anticancer, sterin infections.

Goreja (2003) found that it can be used as a liver tonic, anti-diarrheal appetite. Stimulant, induce lactation in nursing and to fight against contaminants.
Thymoquinone, a secondary metabolite present in the seed, is the important component of the oil which helps in curing most of the infections. In view of its low toxicity, the dark seeds of *Nigella sativa* are used as a nutrient in seasoning breads and pickles. Ali *et al.*, (2008).

**Nigella Sativa**

In various varieties of black seeds, a number of potential compounds have been identified and reported. Thymoquinone (30%-48%) thymohydroquinone, dithymoquinone, p-cymene (7%-15%) carvacrol (6%-12%) 4-terpeneol (2%-7%), t-anethol (1%-3%), sequeiterpenoligosolene (1%-8%) α-pinene and thymol are the important essential potential combination. Dark seeds additionally contain different compounds like isoquinoline alkaloids eg. nigellicimine and nigellicimine, N-oxide, and pyrazole alkaloids or indazole ring bearing alkaloids which include nigellidine and nigellicine which are 2 different alkaloid. They similarly contain alpha-hederin, a water soluble pentacyclitriterpene and saponin, a potential anticancer compound. Atta Ur-Rahman 1995.

*Nagella* seeds are a rich source of unsaturated fats like linolic acid, obic acid, bicodadienoic acid and dihonorinolic acid. Tunisian acid Iranian varieties of black seed oils contain plenty of unsaturated fats (palnitric, stearic acid) around 30% or less, α-sitosterol is an important sterol, which represents 44% and 54% of the total sterol followed by stigma sterol (6.5-20%) of total sterols. Mehta *et al.*, (2008).

**Antibacterial activity**

Crude extract of *Nigella* showed promising effect against microbes. The best extracts were the crude alkaloid and aqua gram negative bacteria were more sensitive to the extract than the gram positive bacteria Morsi (2000).
Bakathir and Abbas (2011) showed the antibacterial effect of black seeds in aqueous media in an paper dispersion technique. A reasonable inhibition one was developed against staphylococcus aureus and distilled water served as control. The inhibition was more in seeds from Hadramouf than with seeds from Ehiopia. The positive inhibition might be due to the presence of Thymequinone and melanin.

**Antidiabetic activity**

The blood glucose level is decreased by *Nigella sativa* or α-lipoic acid. The combination of the three components increased the level of insulin and C-pepside. Therefore α-LA, L-Carnitive and *Nigella sativa* will function to after the carbohydrate metabolism in diabetic rats hence similarly accounts for the activity in human also. Najini *et al.*, (2008).

**Anti cancer activity**

Dietary supplements of black seed powder lowers the oxidative stress brought about by oxidized corn oil in rats. Othman *et al.*, 2006.

Thymoquinone was instrumental in causing huge charges on elastase, metallo peroxidase, lipoxygenase, glutathione nitric oxide and SOD (Superoxide dismutase). Oral administration of Thymoquinone decreased the level of inflammation causing components like 1FN-γ IL-6 and increased IL-10. Umar *et al.*, 2012.

Gendy E, et al., 2007 showed that if Nigella seeds are taken as supplements to a level of 10% in daily eating regimen than the oxidative stress effects shown by agents like dibutylamine and sodium nitrate is restored by bringing in the normal levels of glutathione and nitric oxide.
2.8.4. *Mucuna prureins*

*M prureins* is used as an essential food, fallow and fertilizer in many parts of the universe. As the plant is a legume it fixes nitrogen and also fertilizes the soil. www.tropicaforages.info. (2008).

The plant as a whole is fed to animals as hay or dried seeds. The silage contain 11-23% crude proteins. 35-40% crude fiber and the dried beans contains 20-35% crude protein. www.tropical forages.info (2008).

L-Dopa *M.prureins* are a rich bource of this may be causing nausea vomiting to those who are sensitive to ingestion of high level of L-Dopa. L-Dopa can be removed upto 99% through soaking in boiling water for 40 minutes, changing the water and again soaking in cold water. Pre-boiling ensures removal of toxins in the beans. Further they can be cooked as they desire.

Nyirendra, (2016) In Unani medicine the seeds of *M. prureins* have been used for treating many diseases. It is also used in Ayurvedic medicines. Amin (1996).

The plant and its extracts have been used in the prophylactic treatment of snake bites. The tribal communities makes use of them as a toxin against various snake bites. Research has been done for its effect against cobra, viper, krait. Tan *et al.*, (2009).

In traditional ayurvedic Indian medicine it has long been used in an attempt to treat various oilments including Parkinson’s disease. Katzenschloger, *et al.*, (2003).

**Itching property**

The protein known as mucanain is present on the hairs which are lining the seed pods. This causes severe itching when touched. Reddy *et al.*, (2008).
The flowers are also a source of itchy spicules, the calyse below the flowers is itchy. Toglekar et al., (1963).

**Pharmacology**

The seeds contain about 3%-6% L. Dopa, Google Bork search (2004).


The bioactive chemical L-DOPA is a precusor to several neurotransmitter including dopamine, adrenaline and noradrenaline. Praksh et al., (2001)

L.DOPA along with the significant anti-oxidant properties present in the seeds helps it promote brain health. Katzenschalger et al., (2003).

The antioxidants are helpful for protecting the body against oxidative damage by free radicals. Several research suggests this Yadav et al., (2013).

As L-DOPA is the precusor of dopanine it easily crosses the blood brain barrier where it gets metabolized to dopamine, a neurotransmitter, essential for regulating cognition and also moods way. Amy et al., (2012).

Shuklla et al., 2010 performed a study on 120 men who suffered from psychological stress. Supplementation of *M.prureins* markedly reduced stress and also improved fertility issues.

It has been an Ayurvedic therapy for centuries to treat parkinson’s disease with *M. prureins*. Research disease with *M. prureins*. Research shows that L-Dopa in the *M.prureins* seed provides better results compared with synthetic L-Dopa without side effects like nausea, vomiting, and involuntary muscle movement. Tharakan et al., (2007).
2.8.5. **Saraca asoca**

A study published in complimentary therapies in clinical practice, February 2007 identified Ashoka as one of the herbal remedies in remote areas of India, Uttara Kannade District in Western States of Karnataka used by traditional healers to successfully treat “reproductive disorders” Hegde et al., (2007).

Endometriosis is one of the leading cause for infertility in women. Saraca asoca in ayurvedic medicine is used as an outstanding stimulated to the ovarian tissue and endometrium. The success of Asoka in infertility treatment in women is linked to treat endometriosis. Mishra et al., (2013).

Menorrhagia is a condition with heavy menstrual bleeding. **Saraca asoca** dried bark has been used in India for long in treatment of menorrhagia. Bhandary et al., (1995)

The stern bark along with flowers is given as a tonic to ladies with uterine problem. Middle et al., 1985.

Saraca asoca bark is used to treat menstrual disorder and menorrhagia in Srilanka. Satyavati et al., (1970).

The dried bark extract is also used as a refrigent, demulcent, general uterine disorders, regular menstrual pain in abdomen. Gupta Ind Med Red., (1939).

The medicinal plant saraca asoca is one of the foremost plants used from centuries ago to till date. Asoka is one of the legendry and sacree trees of India. In tanil it is called Asogam meaning no grief. http://www.saraca.indica.com/ayurvedic (2001) also known as saraca indica belonging to the family caesalpinaceae.

The plant is found throughout India distributed widely in evergreen forests of India up to an elevation of 750 meters. In Himalaya, Kerala, Bengal and whole
southern region of India it is grown. In Kerala it is found in Patagiri, Kaikatty and Pothundi of Palakkad district. Trisur, Kollam and Karnaur districts. In Himalaya it is found at Gara, Khasi, Lussi Hills. Nurrier \textit{et al.}, (2000).

The dried bark isolates show five liganan glycosides, byoniside, nudipeside, 5-methoxy-9-p-xylo pyranosyl (-)-isolariuciresinol, icariside E3, and three flavanoids epicatechin, epiafzelechin and procyanidin B2, together with $\beta$-sitosterol glucoside, Dhawan \textit{et al.}, 1977.

**Antibacterial activity**

Mathew \textit{et al.}, showed that the ethanol and aqueous (water) extracts of saraca asoc (Rox) de wilde were investigated for invtro antibacterial activity against staphylococcus aureus, psuedomonas aeruginesa, proteus vulgaris, bacillus aereus and klebsiella pneumoniae at 4mg/ml using agar well diffusion method. The extracts showed remarkable broad spectrum antibacterial effect.

**Antimenorrhagic activity**

In India saraca asoca bark is used as a uterine sedative and the functions of the bark are similar to ergot when hot water extracts are given to adult female it stimulates the uterus but without producing contraction. Saha \textit{et al.}, 1961.

In case of Leucorrhea the bark is boiled in water and milk the extract is given to drink. Ali (2008).

**Skin disorders**

Dabur \textit{et al.}, (2007) stated in their work that Asoca exhibited good activity against bacteria makes it effective in treating skin infections. The antioxidant effect
of Ashoka’s flavanoids have been shown to protect the against skin cancer when applied on top.

**Phytochemical and pharmacological importance of saraca indica**

Asoka bark extracts were found to be antimutagenic and genoprotective. This effect was confirmed by a study done by Nag *et al.*, 2013. According to his finding it is seen that both gallic acid and (A) epicatechin are known to have antimutagenic activity.

**Asoka for type 2 diabetes**

Flavanoid fractions of saraca ashoka flowers show antidiabetic activity by inhibiting $\alpha$-glucosidase and $\alpha$-amylase. It also exhibited good antiglycation effect and inhibited good antiglycation effect and inhibited LDL oxidation under invitro conditions. Results of the study reveal flowers help in preventing oxidative stress and other complications associated with diabetes. Prathapan *et al.*, 2012.

**2.8.6. Symplocus racemosa**

(Chopra *et al.*, 1994) *Symplocus racemosa* also known as Lodhra or Lodh is widely used as a female fertility improving drug India. Traditionally the bark is used for therapeutic purpose.

(Chunekar, 2010) Lodhra has been widely used as a therapeutic agent in Ayurvedha traditionally. It is vital as it mitigates the doshas (forces) in our body like vada (gas), Kabha (mucus) and pitta (gall bladder secretions). It is known to alleviate pitta dosha and Kabha dosha. It stops the blood flow and enhances healing of wound.
Lodhra bark is acrid, astringent and helps digestion. It is commonly used to cure diarrhea. Lodhra is used to beat the body heat hence it is sheet vary a (coolant) light quality, Netrashitakara (good for eyes) and Rata dosha Nashaka (blood purifier). (Ragunathan and Mitra 2000)

The bark contains many phyto constituents these secondary metabolites possess medicinal properties to cure uterus related problems like menorrhagia, leucorrhea and other menstrual disorders. According to Ayurveda Lodhra reduces fever and cures bleeding gums. It can be used to treat leprosy and skin diseases. (Chunekar, 2010).

Pharmacological activity

Anti-acne effect

Kumar et al., (2007), proved that Ethanolic extracts of the bark were tested on the growth of propionibacterium acnes. The results from the disc diffusion method showed that the extracts could inhibit the growth. Hence it is investigated it has anti-acne activity.

Anti-inflammatory and analgesic activity

Vijayabaskaran et al., (2010a) showed the bark ethanolic extract against brewer’s yeast induced pyrexia, hence it was evident that bark ethanolic extract have antipyretic activity.

Antioxidant activity

Ravichandran et al (2005) stated that salireposide and benzoylsalirepeside the principle metabolites of the *symplcas racemosa* have potent antioxidant activity.
Antihelminthic activity

Roa et al., (2011), showed that ether, chloroform and ethanol extract of bark was tested on adult earthworm, P. Posthuma the test revealed ethanolic extract has more antihelminthic effect.

Anti-angiogenic activity

The two phycosides isolated from the bark of Lodhra namely (1) Symplo Comoside and (2) Symponoside inhibit thymidine phosphorybase and related angiogenesis. This effect was analysed by Hussain et al., (2009)

Antibacterial activity

Petroleum ether extracts and ethanolic bark extract were tested against three gram negative and three gram positive bacteria. Ethanolic extract of Symplocos racemosa roxb was found to have good antimicrobial activity when compared to petroleum ether. Devmurari (2010c).

Anticancer activity

Raval et al., (2009a) tested the effect of bark extracts of chloroform, ethyl acetate and butanol using XTT salt against one leukemia and one cervical cell line. It was found that butanol extract had maximum cytotoxic effect against be cell line.

Female reproductive disorders

Bhutani et al., (2004) aqueous extract of bark has effect on serum FSH and LH under basal conditions. The aqueous extract oral administration remarkably stimulated serum FSH level along with elevated LH.
Saraswathi et al., (2012) studied the effect of ethanolic bark extracts at two different doses that showed promising result in treating female reproductive disorders induced by cold restraint stress.

Swarup and Umadevi (1998) mentioned the efficacy of *Symplocos racemosa* in uterine disorders.

**Anti-ulcerogenic activity**

Aspirin induced pylorus ligated model were chosen. The pylorus ligated model responded significantly to both aqueous and ethanolic extracts of bark of *Symplocos racemosa* by reducing ulcer index remarkably compared to aspirin induced model. Krishna et al., (2013).

2.8.7. *Murraya Koenigii*

**Introduction**

The plant is a deciduous shrub and is used in traditional system of medicine. Its used as antiemetic, flavoring agents in curry, hence called curry leaf, antidiarrheal, febrifuge, blood purifier. The oil is used topically for burns, bruises and in soap industries. Prajapati et al., (2003).

Green leaves checks vomiting and it is eaten raw to cure dysentry. *M. Koenigii* contains a lot of chemicals that interact in a complex way to show their pharmacodynamic response. The plant has been diagnosed to have anti-oxidative, cytotoxic, antibacterial, antiulcer and cholesterol lowering functions. Ram et al., (2002).
Curry leaves boiled with coconut oil is used as an excellent hair tonic for retaining hair tone and stimulating hair growth. It is used from ancient time as a whole plant or as a part as traditional medicine as home remedy. Rao et al., (2011).

**Antioxidant and free radical scavenging activity**

Ningappa et al., (2008). The (1:1) alcohol water extract of *M. koenigii* showed maximum antioxidant and free-radical scavenging activity.

Mahanimbine IC 50 antioxidant activity was reported by analysis of liposome oxidation model using fluorescence spectroscopy. Ramsewak et al., (1999).

Feeding of curry leaf powder (12 gm) to non-insulin dependent diabetest mellitus patients (NIDDM) showed a significant reduction in fasting blood sugar and post prandical sugar. Khan et al., (1995).

Excellent results were shown for antidiabetic activity of methanolic and aqueous extracts of *M. Koenigii* leaves and fruits in alloxan-induces diabetic rat. Lawal et al., (2008).

**Hepatoprotective activity**

The study by Guptal et al., on *M. Koenigii* leaves extract proved it to be a promising and a rich source of free radical quenchers, mediated through hepatocyte membrane protecting activity together with reduced lipid. This nature is attributed to the combined effect of carbazoles alkaloids-Mahanimbine, Girinimbine, Isomahanimbine, Mahanine, α-tocopherol, ascerbinc acid and mineral contents of the leaf extract.
**Antimicrobial activity**

Chihiro *et al.*, (1993) *M. Koenigii* crude extract of roots showed strong antibacterial activity.

Essential oil and leaf extracts with water were found to have antibacterial function against staphylococcus epidermidis, *S. aureus* and streptococcus species. Srivastava *et al.*, (2001).

**Cardioprotective activity**

Aqueous extracts of curry leaf *M. Koenigii* protected the rat cardiac tissue against cadmium induced oxidative stress. This was possible due to its antioxidant property. Elina *et al.*, (2012).

**Wound healing activity**

There was a marked reduction in the wound area. Aqueous extract of *M. Koenigii* enhanced the wound-healing by reducing the surface area of the wound. Patidar *et al.*, (2010).

**M. Koenigii promote fertility**

Supplementation of *M. Koenigii* with segle marmeols to delayed pubertal heifers showed stimulation of estrus and fertility in more than 50% of the treated heifers. (Gautam Kumar Das *et al.*, 2016).

The steroids, flavanoids, polyphenols, tannin, saponins, glycosides, terpenoids and anthroquinones present in the *Murraya koenigii, saraca asoca, Symlocos racemosa, mucuna prureins* combined formulation was found to have fertility effect. Meenakshi and Kalavathy (2015).
Antipyretic activity

Ethanolic extract of the leaves were investigated on yeast induced pyrexia rats. 500mg/kg showed significant antipyretic activity (P<0.01) Patel et al., (2009).

2.9. Insilico analysis

Plants form a major source of drug for curing many disease. Nowadays people prefer natural drugs due to their efficiency and fewer side effect. Synthetic drugs cause harm and has much ill effects. The phytoconstituents isolated from plants are highly preferably due to their pharmacological properties and safety when seen in comparison to the synthetic drugs. The application of modern methods namely computational techniques play a vital role in search of new potential constituents from plants and to assess their efficiency through designing and developing the lead (drug) by structure based drug designing. SBDD (Green, J. 2003).

Computational docking methods is of increasing importance in the field of SBDD. It predicts the appropriate protein-ligand interaction geometries. Many techniques are available to identify the possible match between proteins. (Lyskov et al., 2008)

The stable complex formed when one molecule is bound to another in preferred orientation which is predicted by a method called docking. (Martin Zacharias et al., 2003)

Three dimensional structure of a given protein sequence (target) can be predicted based on fold assignment, target-template alignment, model building and model evaluation on its alignment to one or more protein structure (template). This method is comparitive modelling. (Marti-Renom et al 2000).
**Protein-protein interaction**

Macromolecules that play an important key role in many biological actions providing support to the cells in the replication of DNA and transcription of DNA to RNA. The intricate behaviour of proteins lie in its role how they interact with each other. Only the primary and secondary structures of proteins are targets for interaction. (Zubay 1998).


The residues forming the interface differs from study to study. (Stites 1997). Janin and coworkers found that in a complexed state of condition a percentage of the area is ‘buried’. Interface areas are calculated based on crystal structures of monomeric proteins and polypeptides. The interface area was found to be from 670 to 4890Å.

Certain critical binding points exist within these areas known as hotspots. Polar residues are present at these regimes. (Hu *et al.*, 2003).

**Peptidomimetics**

Organic molecule that mimic the action of peptides are peptidomimetics. Mimicking or disrupting protein-protein interaction using small molecule has found an application in drug discovery. (Sipkins *et al.*, 2005).

(Li *et al.*, 2004) found that a mimic of the second mitochondria -derived activator of caspases (Smac) a protein involved in apoptosis, was efficient as the native ligand at 105-106 fold lesser concentrations.
The mannose-binding lectin (MBL) in Lectin complement pathway is necessary for development of immune response in childhood and inflammatory response on oxidatively stressed endothelial cells. Sequence SFGSGFGGGY a decapeptide is found to mimic the ligand MBL, N-acetyl-D-glucosamine (GLCNAC). (Montalto et al., 2001)

The most extensively studied and biological interactions are between integrins and cell adhesion molecules (CAMs). (Cochran 2000).

A large family of heterodimeric surface receptors are integrins found on plasma membranes that interplay cell matrix and cell-cell interactions. (Berman et al 2003 and Newham et al 1996).

Selecting a compound that are more likely to have a predefined target specific activity of interest from the huge collection of dissimilar molecules is a challenge. This has been resolved with powerful computational techniques like docking available structure into the receptor site and pharmacophore searching through geometric relations thought necessary for biological activity. The methodology focuses on ligand and target. Recently these methods have become a standard protocol in the pharmaceutical industry for designing novel drugs. (Marrone et al., 1999).

To assess predictions of protein-protein interactions using the docking methodology is a complicated and long drawn process which requires coordination of many researchers. Mostly in docking algorithms, a docking calculation generally involves, three basic steps: assigning the receptor, and ligand potentials and create a docking assembly performing the calculation, filling the parameters set energy cutoffs and launch and analyzing the result (Janin 2005).
Drug discovery from plants involves a multidisciplinary approach combining botanical, ethnobotanical, phytochemical and biological technique. Drug discovery generally starts with an analysis of binding sites in target proteins, or an identification of structural motifs common to active compounds. It ends with the generation of small molecule leads suitable to further chemical synthetic analysis. In principle the drug discovery process involves three preclinical stages before clinical trials, namely target selection; lead identification and chemical candidate selection. Due to rapid advances in structural biology and computer technology, structure based CADD using docking techniques, virtual screening and library design, along with target structure focusing combinational chemistry, has become a powerful tool in the multi-step process of drug discovery. Opera et al (2007)

Research on chemicals are being found to be increasingly important in cellular functions for example through small molecule modulators and epigenetic. Hence evolved the fields of chemical biology and more recently system chemistry which seek to understand biological systems from a chemistry perspective. Integration of bioinformatics and chemiinformatics will be the solution for this. (Ludlow and Otto, 2008).

In response to the increased demand for new compounds by biologists, chemistry they started using combinatorial chemical technologies to produce more new compounds in shorter periods. From sets of different types of reagents called building blocks combinatral chemistry systematically and repetitively yields a large array of compounds (Hall et al., 2001)
Role of natural product chemistry in cheminformatics

**Definition:** Cheminformatics is the application of informatics methods to solve chemical problems.

Moore and Nisbat (1997) stated that the natural products are highly amenable to the much broader screening presented by the new targets. A natural product is a new natural product chemotypes with curious structures and bioactivities and form potential for sub-library generation of targeted screening. Natural products provide structural information from which virtual compounds can be created by computational chemistry and applied technologies. The modern drug discovery programs relies on the structural versatality of the natural products.