CHAPTER-1

Introduction
Population means the number of inhabitants in a specified territory. During the 20th century two important demographic phenomena have occurred. The first one is the unprecedented growth of human population and the second one is the movement of people from rural to urban areas. This migration of people, which started during the industrial revolution, gained significant momentum over the past 50 years. This has resulted in overcrowding of urban areas.

As per the estimation of United Nations, the world population in the middle of 1991 was 5.385 billion. During this period, the average rate of increase in population was 1.7%. At present the world population is growing at the rate of 176 people per minute, 10,564 people per hour, 253,542 people per day and 92,543,000 people per year. The world population has reached an amazing figure of 6 billion at the end of the last century. If the growth of population continues to increase at this rate, it is estimated that it will cross 7 billion mark by the end of 2022.

Percentage wise, Asian countries contribute 58.8% to the world population, with a growth rate of 2.2%. China has largest population in the world. India is placed second with the contribution of 16% of the population.

In India, population was 344 million in 1947, it was 439 million in 1961, 548 million in 1971 and 844 million in 1991. It has reached the alarming figure of 1 billion in the year 2000. As per the census of 2001, carried out by the Indian government, the population of India is 1,02,70,15,247.

Uttarpradesh ranks first among the states of India, with a population of 138 million as on 1996. Amongst the cities of India, Mumbai has the largest population of 12.57 million and Kolkata comes second with 10.86 million.
Due to the advancement of medical sciences, the cruel balance between the births and deaths maintained by the dreaded diseases like smallpox, cholera, plague, malaria etc. no longer exists. People all over the world now lead healthier and longer life, when compared with the earlier situation.

The present food production is increasing in arithmetic progression, while the population is increasing in geometric progression. When compared with natural and human resources of the country, one can easily conclude that India is overpopulated. Bangladesh, Srilanka, Afghanistan and Pakistan, which are neighbouring countries of India, fall in the same category.

To control the menace of population explosion, many nations have enmarked various programmes of family planning and family welfare. Because of these steps, encouraging demographic progress has been achieved in the last 20 years. Fertility rates have declined worldwide. This has brought down the growth rate of population to some extent. Statistically, the rate of population growth, which was 2.5% per year in 1960, was brought down to 2.3% per year in 1981 and presently it is 2.0% per year. However the base is so large that this reduced rate of growth has very little impact on the population scenario. According to the forecast by experts, the world population may reach 12 or even 14 billion before it stabilizes.

Human settlement existed 1.5 million years ago in Africa as indicated by various evidences such as $^{14}$C dating etc. and others. The following figures indicate the rapid rate at which population is increasing - to reach 1 billion mark of population it took a very long period and happened in the year 1800. It took 130 years, from then, to add one more billion, which occurred in the year 1930. The third billion was added in the shorter period
of time of 30 years, which happened in the year 1960. Then, only 15 years were required to add 4th billion, whereas only 12 years were required for the addition of 5th billion. This unprecedented growth was mainly attributed in the failure in making wide variety of effective, efficient and affordable methods of family planning. The rampant population growth has been viewed as the greatest single obstacle to the social and economic advancement of the majority of the people in the underdeveloped world.

In India overpopulation is due to manifold reasons. However, the major two causes are early marriages and longer span of reproductive activity. The other contributing factors are lack of respect for women and recreational facilities, tropical climate, total beliefs, ignorance, illiteracy, absence of proper welfare schemes and decline of death rate.

The uncontrolled growth of population, results in the creation of various fundamental problems which include unemployment, overcrowding of urban areas, starvation and increase in crime rate. This has also resulted in communal clashes, social inequalities and conflicts.

Population growth will add many problems to the already existing ones, like limited availability of clean water, food, energy, education and job opportunities. If this continues, the process of deforestation, soil erosion and desertification will accelerate. At the end, economic and social foundation of the nation will collapse under the pressure and environmental balance will also be disturbed causing global climate changes.

The spurt in population growth has resulted in urbanization. One half of the world's population today lives in cities that occupy only 2% of the world land. Surprisingly, it consumes 75% of the resources and produce 75% of the waste material in the world. It is expected, by the year 2050, 2/3rd of the world's population will be in urban...
area. Thus large cities are faced with serious basic problems such as depletion of natural resources, mushrooming of slums, traffic congestion etc.

The rural areas continue to suffer from gross inadequacies in health services, sanitation, educational facilities, drinking water problems etc.

According to the report from United Nations Family Planning Association (UNFPA), the rapid population growth is primarily attributed to the following three main reasons

1. Increase in life expectancy
2. Decrease in infant mortality
3. Development of medical science

The continuing high growth rate is also due to ignorance of married couple to use proper methods of fertility regulations. In developing countries, out of 600 million couples, nearly 500 million couples are not using suitable family planning methods. This is also due to the fact that the available methods and services of family planning are too expensive and also sophisticated to meet the demands of the underdeveloped and developing countries.

To solve the above problems, the urgent requirement is to modernize as well as to amplify the present fertility regulation methods. Thus fertility control has become most important and urgent mainstay of all biosocial and biomedical problems faced by mankind.

Improvement and innovation in the technology of birth control are very essential in the present day situation. In the international conference on population and development held in Kairo in the year 1994, it was resolved to focus on the following major programmes

1. The eradication of illiteracy
2. Full employment opportunities for women
3. Achieving the lowest possible rates of infant mortality, and
4. Universal access to the knowledge and affordable methods of family planning to prevent unintended pregnancy.

To achieve the last aim, it is necessary to evolve more acceptable and effective means of contraception, for both male and female with nil or minimum side effects. It is also needed to update the research in human reproduction and fertility regulation, including biochemical research in order to improve safety and efficacy of the existing family planning methods.

A comprehensive discussion of the existing methods of contraception and some newly developed techniques is provided in the following pages.

1.1 Natural Family Planning methods

1.1.1 Abstinence during the fertile phase

This method emphasized on the safe period, which is also known as rhythm method involving the avoidance of sexual intercourse during ovulation period. Ovulation occurs normally on the 14th day of the estrus cycle, in a 28 days normal cycle. However, in some cases, ovulation may occur any time between the 12th and 16th day. Hence, the safe period is calculated from the 1st day of the menstrual period until 8th day of the cycle, which is generally known as pre-ovulation period. The post-ovulation period can also be regarded as the safe period, which normally occurs from 18th day to 28th day.

1.1.2 Withdrawal method (Coitus interruptus)

This is the very common method of family planning, but it is observed that it is quite inefficient in regular practice.
1.1.3 Cervical mucus method

This method is also considered as ovulation method or billing method. Cervical mucus becomes clear, slippery, profuse and smooth, at the time of ovulation. After ovulation, the mucus thickens and lessens in quality. By careful examination of the cervix by females, the sexual intercourse during this period can be avoided.

1.2 Barrier Contraceptives

1.2.1 Condom

The use of condoms is the most widely used method of contraception. The developments in technology have produced extra thin membrane sheaths, marketed in a variety of colours, with or without lubricants under different trade names. These are commonly called as “Nirodh”, which are easily available in market even in rural areas. No medication is required for this method either by male or female. Condoms have a satisfactory efficacy when used properly. The additional advantage of using condoms is that it prevents the transmission of venereal diseases and AIDS.

1.2.2 Diaphragms

These are used by females as the sacks to cover the passage of the sperms to the cervix. It has more failures than success. This is because of the fact that the sizes of diaphragm vary and desired fitness is not achieved.

1.2.3 Spermicidal agents

It has been recommended to use foams, creams and jellies containing spermicidal agents for the prevention of pregnancy. The spermicidal agents are "Surface active agents", which attach themselves to spermatozoa and inhibit oxygen uptake and kill sperms. The spermicidal agents contain surfactants such as octoxynol, nanoxynol-9 and
menfegol. Recently a new agent ORF 13900 has been introduced in market, which agglutinates sperms and thus acts as spermicidal agent\textsuperscript{13}.

1.2.4 Douching

The dutch cap, cervical cap, dumas cap, contra cap and vaginal sponge are widely used barrier devices today for the purpose of immediate postcoital douching of the vagina with spermicidal solution, to wash away the sperms.

1.3 Intrauterine Contraceptive Devices (IUD)

The antifertility action of a foreign body in the uterus was known since ancient times in India. IUD were introduced in the family planning method about 30 years back. IUD is an effective and safe method of contraception. It prevents the implantation of blastocyes in the uterus. A variety of IUDs like Lippe’s loop, Dalken Shield, Soonawala Device, differing in shape have been proposed. Most of these are made up of silastic polymers with or without metallic component. However, this method suffers from major drawbacks like bleeding disorders, pain and expulsion. These side effects have been reduced in the second generation of IUD. This contains copper wire, known as Cu-IUD and the Cu-Ag IUD\textsuperscript{14}. These are marketed in the trade names like Copper-T, Copper-T-200, TuCu-220c, TuCu-380 Ag, Nova-T, ML-Cu-250, ML-Cu-375.

1.4 Contraceptive Steroids (Oral Contraceptives)

Existence of a feedback control between the steroid hormones produced by ovaries and pituitary gonadotrophins which stimulates their synthesis, give rise to the property which forms the basis of utilizing progestogens and estrogens to inhibit the secretion of gonadotrophins and thereby block the ovulation.
The natural hormones, estradiol and progesterone, which are not employed due to their very short biological half-life. In place of these, synthetic steroids with estrogenic and progestogenic activity are used. In earlier days, these drugs were administered orally in the form of oral pills containing a combination of progestones with little amount of estrogens. Now a days these oral pills are available in three types.

i). An orally active progestogen, which contains 19-nor testosterone or 17-hydroxyprogesterone derivatives. These pills suppress pituitary hormone FSH and LH and thereby prevent ovulation.

ii). Combined oral pills containing either ethinyl estradiol or mestranol\textsuperscript{15}.

iii). Triphasic combined pills-These have been recently introduced and normal preparations contain ethinyl estradiol (EE2) and levonorgestrel (LNG).

Many side effects have been attributed to the use of oral contraceptives. Cardiovascular side effects and induction or promotion of tumors are more concerned ones. To overcome this difficulty, injectible contraceptive steroids have been evolved in recent times. The steroids commonly used are methoxy progesterone acetate or nor-ethindrone acetate.

1.5 Interceptive Agents (Post-coital Agents)

These agents interfere with postovulatory events leading to pregnancy and are, therefore, called as "interceptives". Ethinyl estradiol + norethisterone or levonorgestrel, ethinyl stilbesterol, mifepristone (Ru. 486) are the common examples of interceptives. These steroids have high affinity for the progesterone receptors. They act by blocking the action of progesterone on the endometrium.
Prostaglandins act by virtue of their luteolytic effect on the ovary and increased mobility effect on fallopian tube and the uterus, which prevents implantation and induce menstruation.

1.6 Immunological methods

In this method antibodies to sperm antigens are produced by introduction of enzymes like lactate dehydrogenase, hyaluronidase and acrosin. These cause immobilization and destruction of sperms. Inhibin, an anti-FSH vaccine is also under trial. Temporary sterility can be evoked by the use of β subunits of HCG (33 µg). Zona pellucida plays an important role in implantation. If zona pellucida antibodies are developed, which either prevents sperm penetration in the ovum or shedding of zona after fertilization, it can evoke antifertility.

1.7 Sterilization (male and female)

The sterilization operation is undertaken with primary objective of preventing further pregnancy permanently. In tubectomy and vasectomy, the continuity of the duct meant for the transport of ovum and spermatozoa respectively are interrupted. The Minilap Pomeroy technique is considered a revolutionary procedure for the female sterilization. Laproscopic fulgarition is becoming more popular. It is highly effective and very quick. However, these methods have many side effects and also psychological complaints of diminution of sexual vigor and impotency. To overcome these drawbacks, new developments and improvements of the presently available methods have been devised, amongst which, the following two are the most important ones.
1.7.1 The subdermal implants norplant

In this method, a set of six celastic capsules filled with progesterone-levonorgestryl, are introduced beneath the skin under light anaesthesia. The release of the steroid at a steady rate ensures effective contraception for nearly 5 years. These can be used by young women, who require contraception for a longer time and also want to retain the option of another pregnancy.

1.7.2 Progestin release IUD

These are the new methods, which are still in trial stages.

1.7.2.1 Analogues and Antagonist of Luteinizing Hormone Release Hormone (LHRH)

Daily administration of the synthetic analogues of LHRH having prolonged biological half-life, by systematic injections or nasal spray results in blockage of ovulation in the females.

1.7.2.2 Gossypol

This compound was used by an accident in China by several thousands of males causing azospermia. This compound was extracted from the seeds of cotton. It binds with sperm proteins and causes hypokalemia in human beings. However, due to low efficacy versus toxicity ratio in conventional experiments, it is not likely to be approved for human usage.

\[
\text{Gossypol}
\]
1.7.2.3 Prostaglandins and Antiprogestrone compounds for menstrual regulation and termination of pregnancy

These are contraceptive vaccines, which are still in the stage of experimental developments. In all probabilities this may emerge as the most advanced birth control vaccine.

1.8 Herbal options to control fertility

Most of the methods mentioned above are effective. However, none of them is free from one or the other drawback either in the form of side effects or complications in its use. Therefore vigorous and sincere attempts are being made for the improvement of these existing methods. Simultaneously new techniques of fertility regulations are being constantly explored. The encouraging fact is that the demand for new methods for fertility control has increased enormously in India. It is because, every newly married couple, rural or urban, educated or uneducated, want to have smaller family norms. Hence, search for harmless and inexpensive oral agents for fertility control in human beings to reduce the population size is more actually felt now than ever before.

Due to severe and long lasting side effects of modern medicines, the people are now looking back to age-old tradition of using herbal medicines for curing various diseases and also for fertility control. Fortunately India has rich heritage of use of medicinal plants for fertility control. In this context, it is appropriate to locate the large number of indigenous plants that are used as oral contraceptives by tribals and other section of people. Many such plants are even recommended in folk medicines, Ayurvedic and Yunani medicines very ancient times. A good number of scientific papers have
been already published related to the use of medicinal plants for antifertility. However, still many more medicinal plants are either less investigated or left uninvestigated.

Encouraged by these facts, many scientists all over the world in general and India in particular, are presently engaged in the search for a safe, acceptable both by male and female, effective, easily administrable, cheap and non-steroidal antifertility agents derived from medicinal plants, which are commonly grown in India and other parts of the world.

Plants have been screened for variety of fertility regulating activities in both females and males. The plants, which exhibit fertility control in females, may possess antiovulatory, antiimplantation, abortifacient and uterine stimulating activities. The plants, which exhibit fertility control in males, may possess androgenic, antiandrogenic, spermicidal and antispermatogetic activities.

Research on antifertility activity of Indian medicinal plants has been reviewed exhaustively by Choudhury and Haq, Kamboj and Dhawan, Sathyavathi and Bhargava.

In this context, it is felt appropriate and necessary to gather information on such medicinal plants related to fertility control. However, detailed discussion on such plants is not within the limit of this thesis. Hence, a brief account of Indian medicinal plants, used for fertility control is given in the following pages.

1.8.1 Medicinal plants showing antiovulatory activity

Some of the medicinal plants available in India have been shown to possess antiovulatory activity. The list of such plants is given in Table-1.1 along with the parts used with relevant references.
Table-1.1 Plants showing antiovulatory activity.

<table>
<thead>
<tr>
<th>Name of the Plant</th>
<th>Part used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albizia lebbeck</td>
<td>seeds</td>
<td>28</td>
</tr>
<tr>
<td>Aloe barbadensis</td>
<td>leaves</td>
<td>29</td>
</tr>
<tr>
<td>Capsella bursa-pastoris</td>
<td>leaves and dry powdered plant</td>
<td>30</td>
</tr>
<tr>
<td>Mentha arvensis</td>
<td>leaves</td>
<td>31</td>
</tr>
<tr>
<td>Polygonum hydropiper</td>
<td>root</td>
<td>31</td>
</tr>
<tr>
<td>Randia dumetorium</td>
<td>fruits, seeds and pulp</td>
<td>32</td>
</tr>
<tr>
<td>Solanum khasianum</td>
<td>whole plant</td>
<td>33</td>
</tr>
<tr>
<td>Taxus baccata</td>
<td>leaves</td>
<td>34</td>
</tr>
<tr>
<td>Vitex negundo</td>
<td>seeds</td>
<td>35</td>
</tr>
</tbody>
</table>

Vohra and Khan\(^28\) isolated some saponins from the seeds of *Albizia lebbeck* and shown them to possess antiovulatory activity. Aqueous extracts of leaves of *Aloe barbadensis*\(^29\) and dry powder of the plant *Capsella bursa-pastoris*\(^30\) are also shown to exhibit considerable antiovulatory activity. Similarly, extract of leaves of *Mentha arvensis*\(^31\), petroleum ether extract of the root of *Polygonum hydropiper*\(^31\), ethanolic extracts of the fruits and seeds of *Randia dumetorium*\(^32\), ethanolic extract of the whole plant of *Solanum khasianum*\(^33\), aqueous extract of leaves of *Taxus baccata*\(^34\) and seeds of *Vitex negundo*\(^35\) showed potent antiovulatory activity in albino rats.

1.8.2 Medicinal plants showing antiimplantation activity

The survey of literature revealed that there are variety of medicinal plants, which exhibit antiimplantation activity. Some of such plants are listed in Table-1.2 and discussed in brief.
**Table 1.2 Plants showing antiimplantation activity.**

<table>
<thead>
<tr>
<th>Name of the Plant</th>
<th>Part used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abroma augusta</em></td>
<td>root</td>
<td>36</td>
</tr>
<tr>
<td><em>Achrostichum aureum</em></td>
<td>whole plant</td>
<td>37</td>
</tr>
<tr>
<td><em>Allium sativum</em></td>
<td>bulbs</td>
<td>36</td>
</tr>
<tr>
<td><em>Artabotrys odoratissimum</em></td>
<td>leaves</td>
<td>38</td>
</tr>
<tr>
<td><em>Areca catechu</em></td>
<td>nuts</td>
<td>39-40</td>
</tr>
<tr>
<td><em>Artemisia scoparia</em></td>
<td>whole plant</td>
<td>41</td>
</tr>
<tr>
<td><em>Butea frondosa</em></td>
<td>seeds</td>
<td>42</td>
</tr>
<tr>
<td><em>Butea monosperma</em></td>
<td>flowers</td>
<td>42</td>
</tr>
<tr>
<td><em>Caesalpinia decapetala</em></td>
<td>aerial parts</td>
<td>43</td>
</tr>
<tr>
<td><em>Calatropis procera</em></td>
<td>root</td>
<td>44</td>
</tr>
<tr>
<td><em>Carica papaya</em></td>
<td>seed oil, seeds, unripe fruits</td>
<td>45</td>
</tr>
<tr>
<td><em>Cicer arietinum</em></td>
<td>seed oil</td>
<td>42</td>
</tr>
<tr>
<td><em>Costus speciosus</em></td>
<td>rhizomes</td>
<td>46</td>
</tr>
<tr>
<td><em>Cuminum cyminum</em></td>
<td>seeds</td>
<td>47</td>
</tr>
<tr>
<td><em>Curcuma longa</em></td>
<td>rhizomes</td>
<td>48</td>
</tr>
<tr>
<td><em>Cyperus rotundus</em></td>
<td>rhizomes</td>
<td>49</td>
</tr>
<tr>
<td><em>Dacus carota</em></td>
<td>seeds</td>
<td>50</td>
</tr>
<tr>
<td><em>Datura quercifolia</em></td>
<td>fruits</td>
<td>51</td>
</tr>
<tr>
<td><em>Desmodium gangeticum</em></td>
<td>seeds</td>
<td>52</td>
</tr>
<tr>
<td><em>Dieffentachia amoena</em></td>
<td>leaves</td>
<td>53</td>
</tr>
<tr>
<td><em>Embelica ribes</em></td>
<td>berry</td>
<td>54</td>
</tr>
<tr>
<td><em>Ensete superbum</em></td>
<td>seeds</td>
<td>55</td>
</tr>
</tbody>
</table>
The root of *Abroma augusta* has been reported to possess estrogenic activity in female albino rats\(^{36}\).
Dhar et al., investigated the antifertility activity of the ethanolic extract of the plant *Achrostichum aureum* in female albino rats. They observed that the water-soluble fraction of ethanolic extract exhibited very significant antiimplantation activity\(^\text{37}\).

Investigation of the nuts of *Areca catechu* revealed that petroleum ether extract, ethanolic and aqueous extracts of nuts possess antiimplantation activity in albino rats\(^\text{39-40}\).

The seeds of *Butea frondosa* and the flowers of *Butea monosperma* were shown to exhibit considerable antiimplantation activity when tested on albino rats\(^\text{42}\).

Ethanolic extract of *Caesalpinia decapetala*, administered orally on days 1-8, postcoitum, at 500 mg/kg dose exhibited significant contraceptive activity in female hamster but devoid of any estrogenic activity\(^\text{43}\).

Kamath et al., have tested the effect of ethanol extract of the root of *Calatropis procera* in albino rats, in order to explore its hormonal and antifertility activities\(^\text{44}\). A strong antiimplantation activity and uterotropic activity was observed at the dose level of 250 mg/kg.

Keshri et al., carried out extensive research work on *Carica papaya*. Oral administration of the hexane extract of the dry seeds of this plant at the dosage of 1 gm/kg daily, to adult female rats on day 1-10 post coitum, prevented pregnancy in 70% of the animals\(^\text{45}\). Undocumented evidences on this plant, which is used in folk medicine, indicate that this plant has considerable antiimplantation activity in human beings also.

Similarly Khanna and Chowdhary carried out pharmacological investigation of seed and seed oil of *Cicer arietinum*\(^\text{42}\) and observed that these exhibited estrogenic activity in female albino rats.
When screened for antifertility activity, rhizomes of *Costus speciosus* were found to possess significant estrogenic activity in albino rats\(^{46}\). On the other hand the rhizomes of *Cyperus rotundus* were shown to possess antiestrogenic activity\(^{49}\). However, both the plants exhibited antiimplantation activity.

Various extracts of the seeds of *Dacus carota* have been extensively investigated for possible antifertility activity\(^{50}\). The chromatographic fractions of petroleum ether, ethanolic and aqueous extracts of the seeds were also studied. The chloroform and methanol fractions of petroleum ether extract and ethanolic extracts showed 80-100% inhibition of implants in albino rats.

Significant interceptory and estrogenic properties were observed in the plant *Datura quercifolia*. *Datura* lactone isolated from this plant was found to be responsible for these properties\(^{51}\).

Application of Embelin isolated from the fruit of *Embelica ribes* exhibited significant antiimplantation activity\(^{54}\).

![Embelin](https://example.com/Embelin.png)

Saraf and Gomao investigated the root of *Glycyrrhiza glabra* and reported that it exhibited considerable estrogenic activity\(^{56}\).

Extensive research has been carried out on the flowers of *Hibiscus rosa-sinensis* and ethanolic and benzene extracts have been reported to possess antiimplantation activity in women\(^{57}\).
The ethanolic extract of *Hyptis suaveolens* leaves completely inhibited implantation at the dose of 200 mg/kg body weight when administered orally from day 1-7 of pregnancy\(^58\). It was observed that unsaponifiable mass isolated from the leaves and floral parts of this plant showed 20-40% implantation activity at the dose of 250 mg/kg body weight in albino rats. Further research work in this regard showed that antiimplantation activity was due to estrogenic effect.

Antiimplantation activity to the extent of 100% was reported with the fruits of *Illicium anisatum* when administered orally at a dose of 80 mg/kg body weight in albino rats\(^59\). The trans-anethole isolated from the oil obtained from the fruits of this plant was shown to be responsible for this activity. Significant estrogenic activity has been demonstrated by the experiments carried out on young rats.

Dhar et al., have studied the antifertility activity of *Ischochiton campus* and found that its aqueous and methanolic fractions, exhibited considerable postcoital antifertility activity\(^60\). Investigations of the leaves of the plant revealed that ethanolic extract showed 80% and aqueous extract 60% antiimplantation activity in albino rats.

The benzene extract of *Michelia champaka* (anthers) exhibited 67% antiimplantation activity at 1 gm/kg per day dose level\(^61\).

Prevention of pregnancy in Sprague-Dawley rats was observed when n-hexane extract of the seeds of *Nigella sativa* was administered orally at the dose of 2 gm/kg body weight daily from day 1 to 10 post coitum\(^62\).

The leaves of well-known sacred plant *Ocimum sanctum* have been investigated for various biological and pharmacological activities\(^63\). Petroleum ether extract of the
leaves of *Ocimum sanctum* has been found to possess significant antiimplantation activity in albino rats.

It was reported that fruits and root of *Plumbago zeylanica* possess antiimplantation activity when given orally at the dose of 122mg/100 gm weight to albino rats. Further investigations of this plant by Premakumari et al., revealed that Plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone), a crystalline compound from this plant was responsible for such an activity.

![Plumbagin](image)

Various extracts of the tubers of *Peuraria tuberosa* have been tested for their effect on early and late pregnancy in rats, mice, hamsters and guinea pigs. Butanol fraction of the extracts was found to be active due to its inherent hormonal properties. Shukla has described the mechanism of action and toxicological studies of this plant. Puerarin, diadzein and tuberosin were isolated from the chloroform and butanol fractions of ethanolic extract of this plant. The antiimplantation activity exhibited by this plant was attributed to the presence of these compounds.

Shivalingappa et al., have tested the petroleum ether, chloroform, ethanol and aqueous extracts of the aerial parts of the plant *Rivea hypocrateriformis* for antiimplantation activity and pregnancy interruption properties in albino rats. Among
these, ethanolic extract was shown to be most effective in causing significant antiimplantation and interruption of early pregnancy.

Encouraged by various reports mentioned above, Hiremath et al., took up a major research programme of searching non-steroidal antifertility agents from medicinal plants.

The following plants have been investigated for antifertility activity.

1. *Striga densiflora*\\(^70\)

2. *Striga lutea*\\(^71-73\)

3. *Acalypha indica*

4. *Striga orobonchiosides*

They could isolate and identify the different flavones from these plants possessing the following structures.
The extract of the seeds of the plants *Thespesia populnea* and *Trifolium alexandrium* were found to possess significant antiimplantation activity in rats.

Khanna et al. reported that, the aqueous extract of the whole plant of *Uraria lagopodioides* prevented implantation in albino rats when administered orally.

### 1.8.3 Medicinal plants with abortifacient activity

The plants listed in Table-1.3 have been shown to possess abortifacient activity. A brief account of the same is described in the following paragraphs.
Table-1.3 Medicinal plants with abortifacient activity

<table>
<thead>
<tr>
<th>Name of Plant</th>
<th>Part used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achyranthus aspera</td>
<td>stem, bark</td>
<td>76</td>
</tr>
<tr>
<td>Adhatoda vasica</td>
<td>whole plant</td>
<td>77</td>
</tr>
<tr>
<td>Ananas comosus</td>
<td>unripe fruits, juice</td>
<td>78</td>
</tr>
<tr>
<td>Aristolochia indica</td>
<td>root</td>
<td>79</td>
</tr>
<tr>
<td>Curculigo orchoiodes</td>
<td>whole plant</td>
<td>80</td>
</tr>
<tr>
<td>Derris brevipes</td>
<td>whole plant</td>
<td>81</td>
</tr>
<tr>
<td>Gardenia jasminoides</td>
<td>flowers</td>
<td>82,83</td>
</tr>
<tr>
<td>Marsdenia koi</td>
<td>whole plant</td>
<td>84</td>
</tr>
<tr>
<td>Physalis minima</td>
<td>plant without root</td>
<td>85,86</td>
</tr>
<tr>
<td>Pseudolarix kaempferi</td>
<td>root, bark</td>
<td>87-89</td>
</tr>
</tbody>
</table>

Gupta et al., observed that benzene extract of *Achyranthus aspera* exhibited abortifacient effect in rabbits at a single dose of 50 mg/kg\(^*\).

Uterotonic activity in guinea pigs was reported with vasicine, an alkaloid isolated from the plant of *Adhatoda vasica\(^77\). This compound also potentiated prostaglandin induced uterine contractions in rats.

The unripe fruits and juice of *Ananas comosus* were shown to exert abortifacient effect in mice, which was attributed to antiluteotropic activity\(^78\).

Pakrashi and Shaha isolated methyl ether of aristolochic acid from the roots of *Aristolochia indica* and found that it caused 100% abortion effect at a single dose of 60 mg/kg body weight in albino rats\(^79\).
The aerial parts of *Curculigo orchioides* were found to exhibit significant abortifacient activity due to powerful uterine stimulant property of flavone-glycoside isolated from this plant.\(^8^0\)

Badami et al., have shown that the ethanolic extract of *Derris brevipes* exhibited 40% antiimplantation activity when given orally at 600 mg/kg bodyweight.\(^8^1\) However, the results of further investigation suggested that the extract possessed more abortifacient type effect than antiimplantation activity.

The ethyl acetate extract of the flowers of *Gardenia jasminoides* was found to possess significant pregnancy termination effect.\(^8^2\)\(^8^3\) The activity was due to triterpenoids-gardenic acid and gardenolic acid B.

Investigations of aerial parts of *Marsdenia koi* indicated that they can cause termination of early pregnancy in animals.\(^8^4\) Chinese workers Yuan and et al., isolated Marsdekoiside A from this plant.

Ethanolic extract of *Physalis minima* was reported to show significant abortifacient activity. Physalin B155 and Physalin D isolated from this plant were found to be responsible for this activity.\(^8^5\)\(^8^6\).

The root and bark of *Pseudolarix kaempferi* have been investigated extensively for their abortifacient activity.\(^8^7\)\(^8^9\) This activity was due to the presence of pseudolaric acids A \& B, present in this plant.

In addition to theses plants listed in Table-1.1 to Table-1.3, many other plants have been shown to possess considerable antifertility activity in various animals. However, detailed discussion about theses plants is out of the scope of this thesis. Hence, only few plants possessing antifertility activity are listed in Table-1.4.
Table 1.4 Plants with antifertility activity

<table>
<thead>
<tr>
<th>Name of Plant</th>
<th>Part used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Actiniopteris radiata</em></td>
<td>whole plant</td>
<td>90</td>
</tr>
<tr>
<td><em>Adina cordifolia</em></td>
<td>--</td>
<td>91</td>
</tr>
<tr>
<td><em>Ailanthus excelsa</em></td>
<td>leaves, stem bark</td>
<td>92</td>
</tr>
<tr>
<td><em>Andrographis paniculata</em></td>
<td>--</td>
<td>93</td>
</tr>
<tr>
<td><em>Anona squamosa</em></td>
<td>--</td>
<td>94</td>
</tr>
<tr>
<td><em>Artabotrys odoranti</em></td>
<td>leaves</td>
<td>95</td>
</tr>
<tr>
<td><em>Bombax malabaricum</em></td>
<td>root</td>
<td>96</td>
</tr>
<tr>
<td><em>Cassia fistula</em></td>
<td>seeds</td>
<td>97</td>
</tr>
<tr>
<td><em>Catharanthus roseus</em></td>
<td>--</td>
<td>98</td>
</tr>
<tr>
<td><em>Caulerpa taxifolia</em></td>
<td>whole plant</td>
<td>99</td>
</tr>
<tr>
<td><em>Cedrus deodara</em></td>
<td>stem</td>
<td>100</td>
</tr>
<tr>
<td><em>Combretodendron africanum</em></td>
<td>bark</td>
<td>101</td>
</tr>
<tr>
<td><em>Coriandrum sativum</em></td>
<td>seeds</td>
<td>102</td>
</tr>
<tr>
<td><em>Curcuma domestica</em></td>
<td>rhizomes</td>
<td>48</td>
</tr>
<tr>
<td><em>Dictamnus oleifera</em></td>
<td>root bark</td>
<td>103</td>
</tr>
<tr>
<td><em>Dysdercus koenigii</em></td>
<td>--</td>
<td>104</td>
</tr>
<tr>
<td><em>Echinops echinatus</em></td>
<td>--</td>
<td>105</td>
</tr>
<tr>
<td><em>Ferula jaeschkeana</em></td>
<td>fruits</td>
<td>106</td>
</tr>
<tr>
<td><em>Gleditschia horida</em></td>
<td>--</td>
<td>107</td>
</tr>
<tr>
<td><em>Hagenia abyssinica</em></td>
<td>flowers</td>
<td>39</td>
</tr>
<tr>
<td><em>Ipomoea fistulosa</em></td>
<td>--</td>
<td>108</td>
</tr>
<tr>
<td><em>Juniperious communis</em></td>
<td>fruits</td>
<td>109</td>
</tr>
<tr>
<td>Plant Name</td>
<td>Part(s) Described</td>
<td>Page(s)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td><em>Lygodium flexosum</em></td>
<td>whole plant</td>
<td>110</td>
</tr>
<tr>
<td><em>Malvavisens conzatii</em></td>
<td>flowers</td>
<td>111</td>
</tr>
<tr>
<td><em>Mallotus philippensus</em></td>
<td>glands, hairs from the capsules</td>
<td>112,113</td>
</tr>
<tr>
<td><em>Marsdenia oreophila</em></td>
<td>stem</td>
<td>114</td>
</tr>
<tr>
<td><em>Momordica charantia</em></td>
<td>root, leaves</td>
<td>115</td>
</tr>
<tr>
<td><em>Momordica linn</em></td>
<td>leaves</td>
<td>115</td>
</tr>
<tr>
<td><em>Murraya paniculata</em></td>
<td>root</td>
<td>116</td>
</tr>
<tr>
<td><em>Nelumbo nucifera</em></td>
<td>seeds</td>
<td>117</td>
</tr>
<tr>
<td><em>Piper chaba</em></td>
<td>fruits</td>
<td>118</td>
</tr>
<tr>
<td><em>Polygonum stenophyllum</em></td>
<td>root</td>
<td>119</td>
</tr>
<tr>
<td><em>Podophyllum peltatum</em></td>
<td>root</td>
<td>120</td>
</tr>
<tr>
<td><em>Salvia fruiticosa</em></td>
<td>--</td>
<td>121</td>
</tr>
<tr>
<td><em>Seigesbeckia glabrascens</em></td>
<td>--</td>
<td>122</td>
</tr>
<tr>
<td><em>Senecia vulgaris</em></td>
<td>--</td>
<td>123</td>
</tr>
<tr>
<td><em>Sida carpinifolia</em></td>
<td>--</td>
<td>124</td>
</tr>
<tr>
<td><em>Spondias cythera</em></td>
<td>bark</td>
<td>125</td>
</tr>
<tr>
<td><em>Sophera japonica</em></td>
<td>whole plant</td>
<td>126</td>
</tr>
<tr>
<td><em>Stephania herandiifolia</em></td>
<td>rhizomes</td>
<td>127</td>
</tr>
<tr>
<td><em>Tabernaemontana heyneana</em></td>
<td>--</td>
<td>128</td>
</tr>
<tr>
<td><em>Tripterygium wilfordii</em></td>
<td>--</td>
<td>129</td>
</tr>
<tr>
<td><em>Wilbrandia species</em></td>
<td>rhizomes</td>
<td>130</td>
</tr>
</tbody>
</table>
1.8.4 Medicinal plants for male antifertility activity

The search for male contraceptives began in 1950. The researchers all over the world, who are working in this direction, aimed at the following aspects of male contraception.

a) Prevention of spermatogenesis.

b) Interfering with the storage of sperms and maturation.

c) Prevention of the transport of sperms through vas deferens.

d) Changing the constituents of the seminal fluid.

Most of the work carried out in this connection was devoted to prevent spermatogenesis. Surgical vasectomy, non-scalpel vasectomy and chemical occlusion of vas deferens are receiving active attention at present. Follicle Stimulating Hormone and sperm surface protein are considered as immunogens and hence has led to the development of vaccines.

An ideal male contraceptive is the one, which maintains normal level of testosterone, with simultaneous decrease in the sperm count. However, many of the contraceptives for males tend to lower the testosterone level, which suppresses the potency of the contraceptive.

Many compounds were reported to possess male antifertility activity ranging from alkylating agents to gossypol but none of them are free from toxicity. Surgical methods even though successful, have the major drawback in the form of creating weakness, loss of sexual activity etc.
Hence, researchers are looking at the use of medicinal plants for male antifertility activity. But scientists are not successful in getting the reproducible results from medicinal plants.

Several plants have been identified to possess male antifertility effect. Some of these plants are listed in Table-1.5.

**Table-1.5 Medicinal plants possessing male antifertility activity**

<table>
<thead>
<tr>
<th>Name of the plant</th>
<th>Part used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abrus precatorius</em></td>
<td>seeds</td>
<td>131,132</td>
</tr>
<tr>
<td><em>Andrographis paniculatus</em></td>
<td>--</td>
<td>133</td>
</tr>
<tr>
<td><em>Austroplenckia populnea</em></td>
<td></td>
<td>134</td>
</tr>
<tr>
<td><em>Azadirachta indica</em></td>
<td>seed oil</td>
<td>135</td>
</tr>
<tr>
<td><em>Bambusa arundinacea</em></td>
<td>--</td>
<td>136</td>
</tr>
<tr>
<td><em>Barleria prionitis</em></td>
<td>root</td>
<td>137</td>
</tr>
<tr>
<td><em>Carica papaya</em></td>
<td>seeds</td>
<td>138-142</td>
</tr>
<tr>
<td><em>Celastrus paniculatus</em></td>
<td>seeds</td>
<td>143</td>
</tr>
<tr>
<td><em>Colebrookia oppositifolia</em></td>
<td>leaves</td>
<td>144</td>
</tr>
<tr>
<td><em>Martynia annua</em></td>
<td></td>
<td>145</td>
</tr>
<tr>
<td><em>Mentha arvensis</em></td>
<td>leaves</td>
<td>146</td>
</tr>
<tr>
<td><em>Mondia whitei</em></td>
<td>--</td>
<td>147</td>
</tr>
<tr>
<td><em>Mucuna urens</em></td>
<td></td>
<td>148</td>
</tr>
<tr>
<td><em>Piper betel</em></td>
<td>--</td>
<td>149</td>
</tr>
<tr>
<td><em>Quassia amara</em></td>
<td></td>
<td>150</td>
</tr>
<tr>
<td><em>Sarcostemma acidum</em></td>
<td></td>
<td>151</td>
</tr>
<tr>
<td><em>Solanum lycocarpum</em></td>
<td>--</td>
<td>152</td>
</tr>
<tr>
<td><em>Tripterygium hypoglaucum</em></td>
<td>--</td>
<td>153</td>
</tr>
<tr>
<td><em>Tripterygium wilfordii</em></td>
<td>--</td>
<td>154-160</td>
</tr>
</tbody>
</table>
Rao and Sinha investigated male antifertility effects of ethanolic extract of seeds of *Abrus precatorius* Linn. in male albino rats. The post-testicular antifertility effects of this plant received attention by Sinha.

A well-known plant, *Andrographis paniculatus*, has been shown to exhibit significant male antifertility activity.

Mazaro et al., studied aqueous methanolic extract of *Austroplenckia populnea* for male antifertility activity. They observed that sperm concentration in cauda epididymis was decreased significantly at the dose of 500 mg/kg/day.

An alternative approach to vasectomy has been investigated in detail by Upadhyay et al., and they arrived at the conclusion that oil obtained from the plant *Azadirachta indica* can be effective by single intra-vas administration.

Gupta et al., carried out antifertility studies of the root extract of *Barleria prionitis* and leaf extract of *Colebrookia oppositifolia* in male albino rats with special reference to testicular cell population dynamics.

It has been reported that the seeds of the *Carica papaya* inhibit motility of sperms when administered orally. Pathak et al., and several other researchers directed their research work on the extracts of this plant for male antifertility activity. The chromatographic fraction of the chloroform extract eluted with benzene exhibited maximum activity.

The seed extracts of *Celastrus paniculatus* have been shown to possess antispermatogenic action in male albino rats with reversible changes in the liver.
Investigations on the effects of ethanol extract (50%) of *Martynia annua* root on reproduction in male rats revealed that, there is dose related reduction in the testicular sperm count, epididymal sperm count and motility.

Antifertility investigation and toxicological studies of petroleum ether extract of the leaves of *Mentha arvensis* in male albino mice has been reported by Sharma and Jacob.

Watcho et al., during their investigation for male antifertility agent observed that *Mondia whitei* L. has been associated with reversible antispermatogenic and antifertility activity.

Udoh et al., tested the effect of seeds of *Mucuna urens* on the gonads and sex accessory glands of male guinea pigs and found them to be potential male antifertility agents.

Similarly, the extracts of *Piper betel* L. have been shown to possess reversible antifertility effect.

Parveen et al., have tested the chloroform extract of the bark of *Quassia amara* for its impact on male reproductive system in albino rats. A marked decrease in the sperm count, motility, and viability was observed in sperm collected from the cauda epididymis of treated animals when the extract was administered daily for 15 days in the form of intramuscular injections.

It has been reported that methanol extract (70%) of the stem of *Sarcostemma acidum*, arrests spermatogenesis in male rats without noticeable side effects.

The plants *Solanum lycocarpum* and *Tyipterygium hypoglauca* have been investigated for male antifertility activity.
Chinese researchers investigated antispermatogenic effect of *Trypterygium wilfordii*. They isolated multiglycosides from this plant, which are responsible for antispermatogenic activity. A series of research papers by group of these scientists have been published\textsuperscript{154-160}.

### 1.9 Synthetic antifertility agents

Apart from plant extracts, various synthetic compounds also have been tested and proved to have antifertility activity in both female and male. Some of the compounds with promising activity are listed in the following Tables.

#### 1.9.1 Synthetic female antifertility agents

Synthetic antifertility agents interfering with different phases of reproduction have been brought to light, which can be classified under different headings as follows.

#### 1.9.1a Synthetic agents interfering with estrous cycle

The compounds listed in Table-1.6 have been reported to disturb estrous cycle. However, the exact mechanism of their action is not yet established with certainty.

**Table-1.6 Agents interfering at estrous cycle and / or reducing fertility**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>human female</td>
<td>161</td>
</tr>
<tr>
<td>Alkylendiamine derivatives</td>
<td>house fly</td>
<td>162</td>
</tr>
<tr>
<td>Chloroguanide</td>
<td>Rat</td>
<td>163</td>
</tr>
<tr>
<td>Dimethylphosphate</td>
<td>Rat</td>
<td>163</td>
</tr>
<tr>
<td>Genistein and related compounds</td>
<td>domestic animals</td>
<td>164</td>
</tr>
<tr>
<td>Mimosine</td>
<td>Rat</td>
<td>165</td>
</tr>
<tr>
<td>Nikoceptin and Galatoceptin</td>
<td>human female</td>
<td>166</td>
</tr>
</tbody>
</table>
1.9.1b Synthetic agents interfering with development of ova

Antimitotic agents included in the Table-1.7 are reported to interfere with the development of ova by causing the degeneration of cleaving egg.

Table-1.7 Agents interfering with development of ova

<table>
<thead>
<tr>
<th>Agent</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Azauridine</td>
<td>human female</td>
<td>167</td>
</tr>
<tr>
<td>2-Deoxy-D-glucose</td>
<td>rabbit</td>
<td>168</td>
</tr>
<tr>
<td>Diethyl stilbestrol and derivatives</td>
<td>rodents</td>
<td>163</td>
</tr>
<tr>
<td>Methallibure</td>
<td>rat</td>
<td>169</td>
</tr>
<tr>
<td>Staphylococcal α-toxin</td>
<td>rabbit</td>
<td>167</td>
</tr>
</tbody>
</table>

It is well established that oral administration or injection of non-steroidal estrogens after coitus, interfere with the tubal transport of ova in several rodent species. In this process, alterations in the tubal mobility, fluid volume, ciliary movement and some metabolic incompatibility between ova and tubal milieu may be involved. The exhaustive work carried out in this connection has been reviewed systematically by Pincus.\textsuperscript{163}
1.9.1c Synthetic agents having antiimplantation activity

Many synthetic compounds have been reported to inhibit implantation in rats on post coital administration. Some of these compounds are listed in Table-1.8.

**Table-1.8 Synthetic agents having antiimplantation activity**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphen, MRL-37</td>
<td>rhesus monkey, rat</td>
<td>170</td>
</tr>
<tr>
<td>2,3-Diphenyldienes</td>
<td>rodents</td>
<td>171</td>
</tr>
<tr>
<td>1,2-Diphenyl-3,4-dihydronaphthalenes</td>
<td>rodents, rhesus monkey</td>
<td>171</td>
</tr>
<tr>
<td>Diethyl stilbestrol, Dimethyl stilbestrol</td>
<td>rat</td>
<td>172</td>
</tr>
<tr>
<td>2,3-Diphenylindoles</td>
<td>rat</td>
<td>173</td>
</tr>
<tr>
<td>3,4-Diphenyl coumarins</td>
<td>rat</td>
<td>174</td>
</tr>
<tr>
<td>3,4-Diphenyl chromanes</td>
<td>rat</td>
<td>175</td>
</tr>
<tr>
<td>1,2,3,4-Tetrahydro-2,2-diarylnaphthalene</td>
<td>rat</td>
<td>176</td>
</tr>
<tr>
<td>2,3-Diphenylacrylophenones</td>
<td>rat</td>
<td>177</td>
</tr>
<tr>
<td>Isoflavone derivatives</td>
<td>rat</td>
<td>173</td>
</tr>
<tr>
<td>Non steroidal estrogens</td>
<td>rodents, rhesus monkey, human female</td>
<td>171</td>
</tr>
</tbody>
</table>
During the last 15 years, extensive research work on animal studies have been carried out. These studies have established that it is possible to prevent pregnancy by variety of non-steroidal compounds. Special attention has been focused on synthesis of potential post coital antifertility compounds with special reference to structure activity relationship studies. Increasing knowledge of the physiological process of fertilization, zygote development and transport and implantation mechanism is providing leads for more rational design for synthesis of new non-steroidal contraceptive agents. These developments would be valuable additions to the existing family planning methods and techniques for birth control.
1.9.2 Synthetic male antifertility agents

The survey of literature reveals that, till today no plant extracts have been found to be authentically useful for male antifertility activity. Hence, researchers have diverted their attention for synthetic compounds with potential male antifertility activity simultaneously with exploration of medicinal plants for such an activity. The synthetic work carried out so far has resulted in the discovery of some new antifertility agents which are listed in the Table-1.9.

Table-1.9 Synthetic male antifertility agents

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Chlorohydrine-3-Cl-7,2-propanediol</td>
<td>178</td>
</tr>
<tr>
<td>6-Cl-6-Deoxyglucose</td>
<td>179</td>
</tr>
<tr>
<td>2,4, Diaminopyrimidines</td>
<td>180</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>181</td>
</tr>
<tr>
<td>17-β-Ethynl estradiol and 9,11-tritiated norethindrone</td>
<td>182</td>
</tr>
<tr>
<td>Ornidazole</td>
<td>183</td>
</tr>
<tr>
<td>4-Methyl-7-hydroxycoumarin, 4-methyl-(tetrahydrobenzo furano)[6,7-b]coumarin</td>
<td>184</td>
</tr>
<tr>
<td>2,3,4,4a,5,9b-Hexahydroindeno(1,2-c)pyridine</td>
<td>185</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>186</td>
</tr>
<tr>
<td>Styrene maleic anhydride</td>
<td>187</td>
</tr>
<tr>
<td>Sulphapyridine, N-1-Me-sulphamilamide, N-1-diethyl Sulphanilamide</td>
<td>188</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>189</td>
</tr>
</tbody>
</table>
The list of compounds mentioned in Table-1.6 to Table-1.9, reveal that the compounds possessing antifertility activity both in male and female belong to different classes of compounds having diverse structures. It is also observed that structure activity relationship studies have not been established for many of the synthesized compounds. These facts encouraged several researchers to synthesize and investigate antifertility activity of new non-steroidal compounds belonging to different classes. Variety of
heterocyclic compounds containing oxygen, nitrogen and sulphur have been synthesized and screened for antifertility activity both in males and females. Some of the important class of compounds discovered so far are listed below.

**Flavones and flavonoids**

Wani\(^1\) et al., and Moersch\(^2\) et al., synthesized several flavones, isoflavones, flavonoids and coumarins and evaluated them for antifertility activity and estrogen receptor binding property.

**Derivatives of benzopyran**

Extensive research work has been carried out by several synthetic organic chemists in connection with the synthesis and evaluation of antifertility activity of benzopyran derivatives.

Ismail et al., have synthesized some novel 4H-benzopyran-4-one derivatives as non-steroidal antiestrogens for their uterotropic, antiuterotropic and antiimplantation activities in mature female albino rats\(^3\). Among the products, the 2-(4′-methoxyphenyl)-7-methoxy-4H-1-benzopyran-4-one exhibited highest antiestrogenic activity to the extent of 65 %.

![Chemical structure of 2-(4′-methoxyphenyl)-7-methoxy-4H-1-benzopyran-4-one](image)

2-(4′-methoxyphenyl)-7-methoxy-4H-1-benzopyran-4-one

Some derivatives of 2,3-diphenyl-4H-oxofuro[3,2-c]benzopyran have been synthesized and evaluated as possible antifertility agents\(^4\).
Sharada et al., have synthesized 2-aroyl-3-methyl-7-phenyl-5H-furo[3,2-g][1]benzopyran-5-ones for their antifertility activity. However, none of these compounds were found to exhibit antifertility activity.$^{194}$

Synthesis of some 9,10-diphenyl-5-oxo-5H-benzofuro[6,5-c]benzopyran have been reported by Rao et al. Considerable anti-implantation activity was observed with some of the newly synthesized compounds.$^{195}$

Rao and Somayajulu have synthesized several benzopyran derivatives and noticed that many synthesized compounds possessed significant anti-implantation activity in rats.$^{196,197}$

**Derivatives of furans, benzofurans and naphthofurans**

Several furan derivatives have been synthesized and when evaluated for in vitro for binding to the estrogen receptor and in vivo for uterotropic and antifertility activities revealed that, 4',17-dioxo-5'H-estra-1(10),4-dieno[3,2-b]furan was capable of inhibiting (3H)E2 binding by 16%, while still eliciting high uterotrophic and post coital antiimplantation activities relative to estradiol.$^{198}$

Substituted furan compounds such as 2,3,4-triphenylfurans and 2,3,4-triphenyl-5-methylfurans have been synthesized and evaluated their antifertility effect on albino rats.$^{199}$

\[
\text{H}_2\text{C}_6\quad\text{C}_6\text{H}_5\quad\text{O}\quad\text{C}_6\text{H}_5
\]

2,3,4-Triphenylfurans

\[
\text{H}_2\text{C}_6\quad\text{C}_6\text{H}_5\quad\text{H}_3\text{C}\quad\text{O}\quad\text{C}_6\text{H}_5
\]

2,3,4-Triphenyl-5-methylfurans
Kar et al., synthesized 2-phenyl-3-diethylpyrrolidinoethoxy-6-methoxy benzofuran hydrochloride and investigated its biological activities. These investigations revealed that, this compound has got antifertility activity when administered orally\textsuperscript{200}.

Several 2,3-diphenylbenzo and 5,6-polymethylbenzofurans, 1,2-diphenyl naphthofurans and many other related compounds have been shown to exert antifertility action\textsuperscript{201}.

Antiuterotrophic activity of some derivatives of benzofurans and napthofurans has been reported in literature\textsuperscript{202}. In this connection, Saksena et al., investigated the pharmacological properties of some benzofurans with special reference to their anti-inflammatory and antifertility activities\textsuperscript{203}.

Tiwari and co-workers carried out an extensive research work on synthesis of antifertility agents. In this connection, they reported the synthesis of diphenynaphtho[1,2-b] and diphenynaphtho[2,1-b]furans\textsuperscript{204}.

**Derivatives of pyridine**

Cook et al., have synthesized analogs of (4aRS, 5SR, 9bRS)-2-ethyl-2,3,4,4a,5,9b-hexahydro-7-methyl-5-p-tolyl-1H-indeno[1,2-c]pyridyne and tested in mice for male antifertility activity. They studied this activity with special reference to the ability of the compounds to reduce testes weight and disrupt spermatogenesis. Some of the tested compounds proved to be effective antifertility agents\textsuperscript{205}.

**Derivatives of pyridazine**

In continuation of the research work for the discovery of potential antiestrogens, Ismail et al., have synthesized few pyridazine derivatives and screened them for antifertility activity\textsuperscript{206}.
Derivatives of quinolines and isoquinolines

Several derivatives of quinoline and isoquinoline have been reported to possess antifertility activity both in male and female. A new series of non steroidal female antifertility agents such as, 1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinolines have been shown to exhibit antifertility activity by Paul et al.

Sangwan and et al., synthesized several 3-Aryl-4,5-dihydro-2-substituted-5-tosyl-2H-pyrazolo[4,3-c]quinolines and evaluated them for their CNS, CVS and antifertility activity. However, none of the compounds were found to possess considerable antifertility activity.

Basic ethers of 1-(4-hydroxyphenyl)-2-phenyl-1,2,3,4-tetrahydroquinoline have been shown to exhibit antifertility activity.

Kulkarni et al., took up a major research programme devoted towards the synthesis of several nitrogen heterocycles having potential antifertility activity. In this regard, they have synthesized 10,12-substituted [1,4]-benzoxazino [3,4]-quinazolin-8-ones, 2-(N,N-substituted-aminomethyl)-3-(2-pyridyl)-4(3H)-oxo-3,1-quinazolines and several derivatives of quinazolin-4-one and screened them for antifertility and anthelmintic activities. The work carried out by these scientists has resulted in several research publications.

Kelkar et al., have synthesized some 2-acetyl-3-aryl-5-tosyl-7/8-H(or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-c]quinolines and tested them for their antifertility activity. In preliminary screening, two of the synthesized compounds have been found to prevent pregnancy at 20 mg/kg dose in female albino rats.
4-Nitroisoquinoline synthesized by Chaudhary has been shown to exhibit considerable antifertility activity\textsuperscript{214}.

Chloroquin, which is generally known as antimalarial drug, has also been shown to exhibit antifertility activity in male rats\textsuperscript{215}.

Winters et al., have tested the pregnancy terminating activity of pyrazolo[1,5-a] indoles and quinolines. The new pyrazoles were found to be more active for abortifacient activity\textsuperscript{216}.

**Derivatives of benzopyranopyridazines**

It is well known fact that when two or more heterocycles are connected to each other, the resulting compounds will be having enhanced pharmacological and biological activities than the individual heterocycles. Hence, Hajela et al., have synthesized some substituted benzopyranopyridazines and pyridazines for their antifertility activity\textsuperscript{217}.

The above facts clearly reveal that compounds possessing both male and female antifertility activity could be obtained from various medicinal plants as well as by the way of synthesis in the laboratory.

The worldwide use of indigenous plant products, to regulate fertility, may indeed prove a rich source of information on a variety of possible new approaches to contraception. Research in traditional medicines and ethnopharmacology, all over the world, has received more attention from the Governments of various countries as well as the World Health Organization. It is widely acknowledged that India has tremendous wealth of medicinal plants. Hence, investigation of medicinal plants for various biological and pharmacological activities and their phytochemical studies is a very fruitful field for further research work.
Kuvempu University, which is situated in the heart of Malnad region, has enormous source of medicinal plants. More than 50% of the flora in this area is useful to mankind for the treatment of diseases starting from simple cold and cough to very complicated diseases like cancer and AIDS.

Survey of literature revealed that not much work has been carried out on these medicinal plants, as regards to their phytochemical investigation and pharmacological studies, available around Kuvempu University area. Many Ayurvedic pandits and Unani hakims of this region have been using some of the medicinal plants for fertility control both for male and female. Moreover there are plenty of unwritten evidences of usage of these medicinal plants in folklore.

These facts encouraged us to enumerate medicinal plants of this area, which are useful as antifertility agents. The same has been presented in Chapter-2.

Several heterocyclic compounds containing furan, benzofuran, naphthofuran, quinoline and isoquinoline moieties in them have been found to possess various pharmacological properties including antifertility activity, as discussed earlier. Many naphthofuran compounds possessing nitrogen heterocycle either in condensed form or in coupled form have been synthesized by well-established procedures in our laboratory. Many of these compounds synthesized have been found to possess wide spectrum of biological and pharmacological activities. Several research papers have been published, describing the synthesis of naphthofuran derivatives and their antimicrobial, anthelmintic, analgesic, antiinflammatory, diuretic and antifertility activities.
From the above discussion it is very clear that the compounds exhibiting antifertility activity possess diversified structures belonging to different classes including heterocyclic compounds. Some of the heterocyclic compounds encompass furan, benzofuran, naphthofuran and pyrimidine ring systems in their structures. This provides extensive field of research work in the direction of synthesis of many heterocyclic systems either condensed or coupled with each other. Encouraged by the wide scope of synthetic research work in this area, it was contemplated to synthesize condensed heterocyclic systems enclosing both naphthofuran and pyrimidine rings and evaluate them for various pharmacological activities and antifertility activity.

For a systematic presentation, the work now carried out is presented on the following lines.

- Enumeration of medicinal plants for antifertility activity in and around Shimoga and Chitradurga.
- Extraction and phytochemical investigation of the plant *Balanites Roxburghii*.
- Analysis of soil.
- Investigation of antifertility activity of the crude extracts in female albino rats.
- Investigation of the crude extracts for antifertility activity in male albino rats.
- Investigation of the crude extracts for other biological activities.
- Separation, isolation and identification of compounds in crude extracts.
- Antifertility activity of pure fraction (both in female and male).
REFERENCES


